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(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; P. O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HERMSMEIER, Mark, Alden** [US/US]; 13 Ramapo Trail, Somerville, NJ 08876 (US). **RAWLINS, David, B.** [US/US]; 219 Vernon Road, Morrisville, PA 19067 (US). **WITYAK, John** [US/US]; 25 Jared Drive, Robbinsville, NJ 08691 (US).

(74) Agents: **DUNCAN, Laurelee** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

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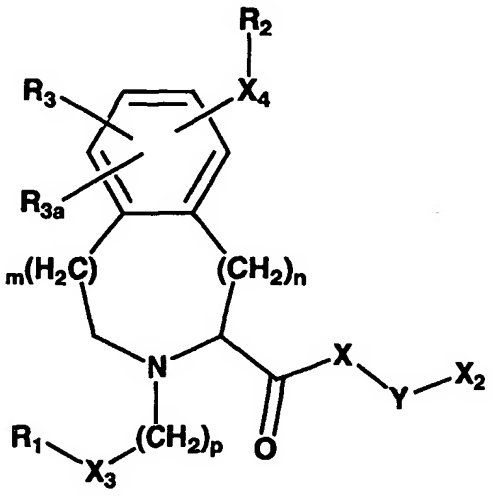
(54) Title: TETRAHYDROISOQUINOLINE ANALOGS AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY



(57) Abstract: Tetrahydroisoquinoline analogs are provided which are modulators of chemokine receptor activity. The tetrahdroisoquinoline analogs thereof have the structure: (Formula I); wherein R?1#191, R?2#191, R?3#191, R?3a#191, X?1#191, X?2#191, X?3#191, X?4#191, m, n and p are as described herein.

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TETRAHYDROISOQUINOLINE ANALOGS AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

This application claims priority from U.S. provisional application serial number 60/346,377 filed November 9, 2001.

Field of the Invention

The present invention relates to tetrahydroisoquinoline analogs which are chemokine receptor modulators, and to methods for treating inflammatory diseases such as asthma, constrictive obstructive pulmonary disease (COPD), inflammatory bowel syndrome, allergic diseases, psoriasis, and arthritis.

Background of the Invention

Chemokines are chemotactic cytokines that are released by a variety of cell types to attract and activate other cell types such as macrophages, T and B lymphocytes, basophils, neutrophils, mast cells, and eosinophils. They are broadly classified as C, CC, CXC, or CX_3C chemokines dependent upon their amino acid sequence. For example, in CC chemokines the first two cysteines in the sequence are adjacent, while in CXC chemokines these cysteines are separated by one or more amino acid residues.

Chemokines bind to specific cell-surface receptors that belong to the family of G protein coupled seven transmembrane domain proteins. Upon ligand binding, chemokine receptors transduce an intracellular signal through the associated trimeric G proteins, resulting in calcium flux, changes in cell morphology, upregulated expression of cellular adhesion molecules, degranulation, and promotion of cell migration.

Chemokine receptors are implicated as key mediators of inflammatory, infectious, and immunoregulatory disorders and diseases, including asthma, COPD, and allergic diseases; rheumatoid arthritis, atherosclerosis,

and psoriasis; solid organ transplant rejection, osteoarthritis, and inflammatory bowel syndrome. To illustrate, the CCR3 receptor appears to be a key mediator in attracting eosinophils and Th2 polarized CD4+ T cells to sites of inflammation in the lung, and also plays an important role in activating these cells. The ligands that bind CCR3 can induce a rapid increase in the intracellular calcium ion concentration (calcium flux), degranulation, increased expression of cell adhesion molecules, and cell migration. Agents that could modulate activity of the CCR3 receptor would have utility in the treatment of disorders and diseases in which eosinophils or Th2 CD4+ T cells appear to play a prominent role. A similar utility has been demonstrated using antibodies specific for the murine CCR3 chemokine receptor. Such antibodies can be used to deplete eosinophils in in vivo inflammatory models in mice.

Several mammalian viruses such as, but not limited to, cytomegaloviruses, herpesviruses, and poxviruses have been shown to express proteins with the binding properties of chemokine receptors in infected cells. In addition, several chemokine receptors have been demonstrated to act as cellular receptors for a variety of viruses, as well as some bacteria, and parasites. Thus, agents which modulate chemokine receptor activity may also have utility in infectious diseases. Examples would include, but not be limited to, blocking of HIV infection of CCR3, CCR5, or CXCR4 expressing cells; or in the prevention of manipulation of the immune response by viruses such as cytomegaloviruses that use a chemokine receptor for cellular infection.

Summary of the Invention

In accordance with the present invention tetrahydroisoquinoline analogs are provided which are chemokine receptor modulators (especially modulators of CCR3) and have the structure

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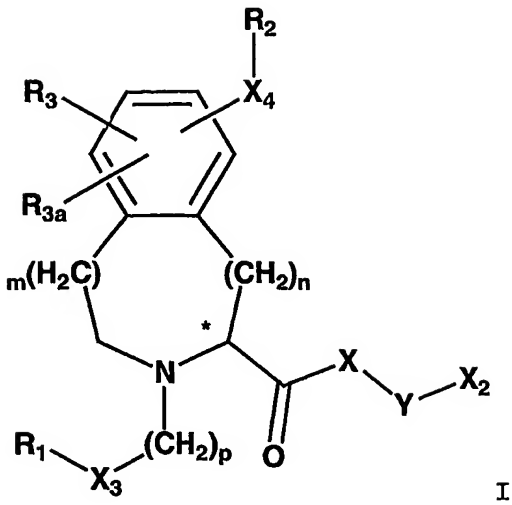


I

wherein R_1 is alkyl, aryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, cycloalkyl,arylcycloalkyl cycloalkylalkyl, cycloalkyl-alkoxy, alkoxyalkyl, alkylthioalkyl, aryloxyalkyl, arylalkoxyalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, or heteroarylalkyl, and where these groups may be optionally substituted with 1 to 3 J1 groups which may be the same or different and the R_1 aryls may be further optionally substituted with 1 to 5 halogens, aryl, $-CF_3$, $-OCF_3$, 1-3 hydroxyls, 2 of which substituents where possible, may be joined by a methylene bridge;

R_2 is H, alkyl, aryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, aryloxyalkyl, arylalkoxyalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkylalkoxy, heteroaryl, or heteroarylalkyl, and where these groups may be optionally substituted with a J1a group and the aryls may be further optionally substituted with 1 to 5 halogens, $-CF_3$, $-OCF_3$, or 1-3 hydroxyls;

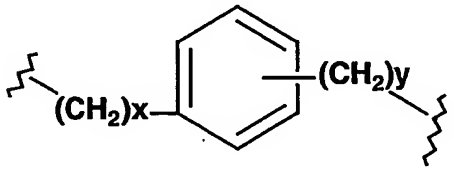
X is a bond, -O-, or $-NR_4-$;

R_3 and R_{3a} are the same or different and are independently selected from H, alkoxy, halogen, $-CF_3$, alkyl, or aryl;

R_4, R_{4a}, R_{4b}, R_{4c}, R_{4d}, R_{4e}, R_{4f}, R_{4g}, R_{4h}, R_{4i}, R_{4j}, R_{4k}, and R_{4l} are the same or different and are independently selected from H, C_1-C_6alkyl, or aryl;

m, n and p are the same or different and are independently 0 or 1;

Y is a bond,



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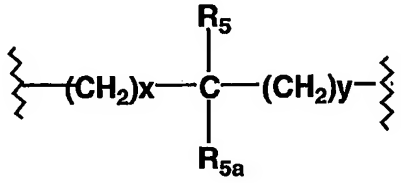

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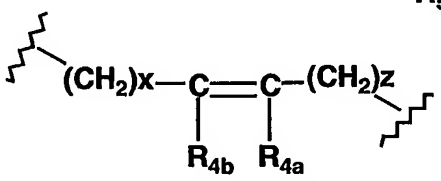
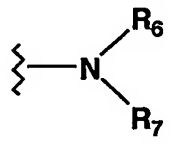


where x and y are the same or different and are independently 0 to 3 and z is 1 to 3;

R_5 and R_{5a} are the same or different and are independently H, alkyl, alkoxy, hydroxyl, halogen, $-CF_3$, aryl, alkaryl, and cycloalkyl; or R_5 and R_{5a} can be independently joined to one or both of R_6 and R_7 groups (see X_2) to form an alkylene bridge of 1 to 5 carbon atoms; or R_5 and R_{5a} can be joined together to form a ring of from 4-7 carbon atoms;

X_2 is aryl optionally substituted with 1 to 3 J1 groups which may be the same or different, cycloheteroalkyl optionally substituted with 1 to 3 J1 groups which may be the same or different, pyridinyl optionally substituted with 1 to 3 J1 groups which may be the same or different,



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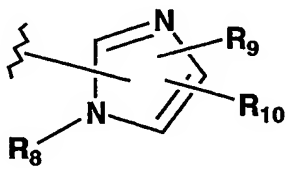

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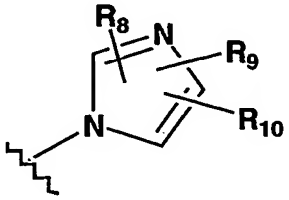


;

R_6 and R_7 are the same or different and are independently H or alkyl where the alkyl may be optionally substituted with halogen, 1 to 3 hydroxys, 1 to 3 C_1-C_{10}alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl,

phenoxy, or C_1-$_6$alkoxycarbonyl; or R_6 and R_7 can together form $-(CH_2)_tX_5(CH_2)_u-$ where X_5 is $-C(R_{4c})(R_{4d})-$, $-C(R_{4c})(NT_1T_{1a})-$, -O- or $-N(R_{4e})-$, t and u are the same or different and are independently 0 to 4;

R_8 is H, C_1-C_6alkyl, $-CF_3$, alkaryl, or aryl, and with the alkyl and aryl groups being optionally substituted with 1 to 3 hydroxys, 1 to 3 C_1-C_{10}alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy or C_1-C_6alkoxycarbonyl;

R_9 and R_{10} are the same or different and are independently H, C_1-C_6alkyl, $-CF_3$, alkaryl, aryl, or halogen, and with the alkyl and aryl groups being optionally substituted with 1 to 3 hydroxys, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-$_6$ alkoxy, phenyl, phenoxy or C_1-C_6 alkoxycarbonyl;

X_3 is a bond, $-C(O)-$, $-C(O)O-$, $-C(O)N(R_{4f})-$, $-S(O)_2-$, or $-S(O)_2N(R_{4f})-$;

X_4 is a bond, -O-, $-OC(O)-$, $-N(R_{4g})-$, $-N(R_{4g})C(O)-$, $-N(R_{4g})C(O)N(R_{4h})-$, $-N(R_{4g})S(O)_2-$, $-N(R_{4g})S(O)_2N(R_{4h})$, $-OC(O)N(R_{4g})-$, $-C(O)-$, $-C(O)N(R_{4g})-$, -S-, $-S(O)_2-$, or $-S(O)_2N(R_{4g})-$;

J1 and J1a are the same or different and are independently nitro, halogen, hydroxyl, $-OCF_3$, $-CF_3$, alkyl, aryl, $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vN(T_{1a})C(O)OT_1$, $-(CH_2)_vN(T_{1a})C(O)N(T_{1a})T_1$, $-(CH_2)_vNT_1(T_{1a})$, $-(CH_2)_vN(T_{1a})SO_2T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)N(T_{1a})T_1$, $-(CH_2)_vN(T_{1a})SO_2N(T_{1b})T_1$, $-(CH_2)_vOT_1$, $-(CH_2)_vSO_2T_1$, $-(CH_2)_vSO_2N(T_{1a})T_1$, $-(CH_2)_vC(O)T_1$, $-(CH_2)_vCH(OH)T_1$, or heteroaryl as defined below, with v being 0-3;

T_1, T_{1a} and T_{1b} are the same or different and are independently H, alkyl, alkenyl, alkynyl, lower alkythioalkyl, alkoxyalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, or cycloalkyl, each of which may be optionally substituted with halogen, hydroxyl, $-C(O)NR_{4i}R_{4j}$, $-NR_{4i}C(O)R_{4j}$, -CN, $-N(R_{4i})SO_2R_{11}$,

-OC(O)R4i, -SO_2 NR4iR4j, -SOR_{11}, -SO_2R_{11}, alkoxy, -COOH, cycloheteroalkyl, or -C(O)OR_{11}; with the proviso that T_1 cannot be hydrogen when it is connected to sulfur, as in SO_2T_1; or T_1 and T_{1a} or T_1 and T_{1b} can together form -$(CH_2)_rX_{5a}(CH_2)_s$- where X_{5a} is -$C(R_{4k})(R_{4l})$-, -$C(R_{4k})(NT_1T_{1a})$-, -O- or -$N(R_{4k})$-, r and s are the same or different and are independently 0 to 4;

R_{11} is C_1-C_6alkyl or aryl;

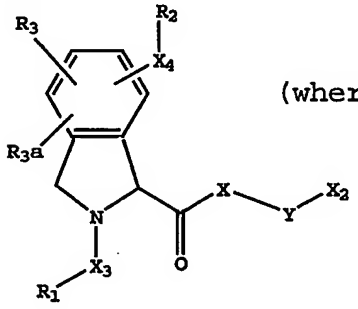
or a pharmaceutically acceptable salt thereof, or a prodrug ester thereof, and including all stereoisomers thereof;

(1) with the proviso that where m is 0 and n is 1, the moiety -X_4-R_2 is other than alkyl or alkoxy and

(2) where X is a bond and X_2 is amino, then m is 1.

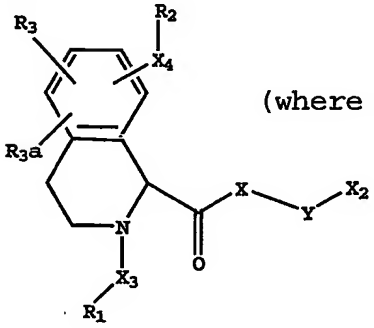
Thus, the compounds of formula I of the invention include compounds of the following structures.

IA



(where m is 0 and n is 0)

IB



(where m is 1 and n is o)

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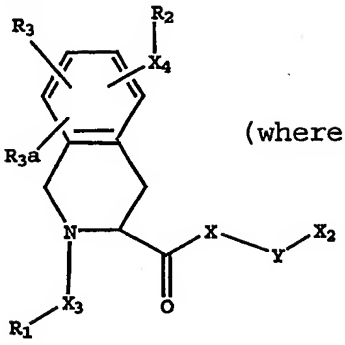

(where m is 0 and n is 1)

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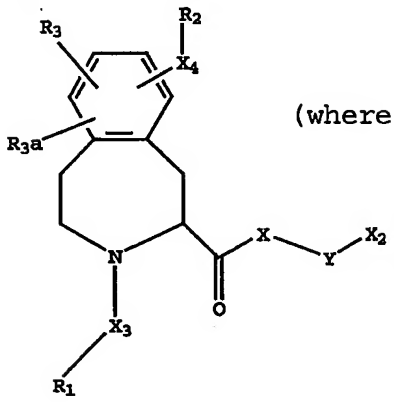


(where m is 1 and n is 1)

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in structural formula I. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof, be included within the ambit of the instant invention. The racemic mixtures may be separated into individual optical isomers employing conventional procedures such as by chromatography or fractional

crystallization. In the case of the asymmetric center represented by the asterisk in formula I, it has been found that compounds with either the R or S configuration are of almost equal activity. Therefore one isomer might be only slightly preferred, therefore both are claimed.

The pharmaceutically acceptable salts of the compounds of formula I of the invention include alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium, as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, ethylenediamine, t-butylamine, t-octylamine, dehydroabietylamine, as well as pharmaceutically acceptable anions such as chloride, bromide, iodide, tartrate, acetate, methanesulfonate, maleate, succinate, glutarate, and salts of naturally occurring amino acids such as arginine, lysine, alanine and the like, and prodrug esters thereof.

In addition, in accordance with the present invention, a method for increasing levels of endogenous growth hormone or increasing the endogenous production or release of growth hormone is provided wherein a compound of formula I as defined hereinbefore is administered in a therapeutically effective amount.

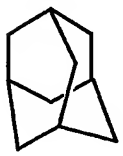
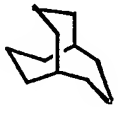
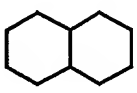
Furthermore, in accordance with the present invention, a method is provided for preventing or treating osteoporosis (improving bone density and/or strength), or treating obesity, or increasing muscle mass and/or muscle strength, or maintenance of muscle strength and function in elderly humans, or reversal or prevention of frailty in elderly humans, wherein a compound of formula I as defined hereinbefore is administered in a therapeutically effective amount.

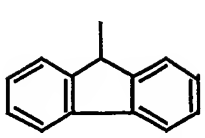
Detailed Description of the Invention

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, more preferably 1 to 6 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 3 substituents including alkyl, aryl, alkenyl, alkynyl, hydroxy, arylalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, arylalkyloxy, alkanoyl, amino, haloaryl, CF_3, OCF_3, aryloxy, heteroaryl, cycloalkylalkoxyalkyl, or cycloheteroalkyl.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 7 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, cyclohexenyl,

 ,  ,  ,  ,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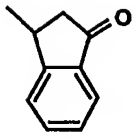
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any of which groups may be optionally substituted with 1 to 3 substituents as defined above for alkyl.

The term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl) and may optionally include one to three additional rings fused to "aryl" (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through available carbon atoms with 1 to 5 halo, 1, 2, or 3 groups selected from hydrogen, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkylalkyl, fluorenyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, oxo, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl, or preferably any of the aryl substituents as set out above.

Preferred aryl groups include phenyl, biphenyl or naphthyl.

The term "aralkyl", "aryl-alkyl" or "aryllower alkyl" as used herein alone or as part of another group refers to alkyl groups as discussed above having an aryl

substituent, such as benzyl or phenethyl, or naphthylpropyl, or an aryl as defined above.

The term "lower alkoxyl", "alkoxyl", "aryloxyl" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

The term "amino" as employed herein alone or as part of another group may optionally be substituted with one or two substituents such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and/or cycloalkyl.

The term "lower alkylthio", alkylthio", "alkylthioalkyl", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

The term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

The term "acyl" as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl $\left(\overset{O}{\overset{\|}{C}}\right)$ group; examples of acyl groups include alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, and the like.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 3 to 12 carbons, and more preferably 2 to 6 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl,

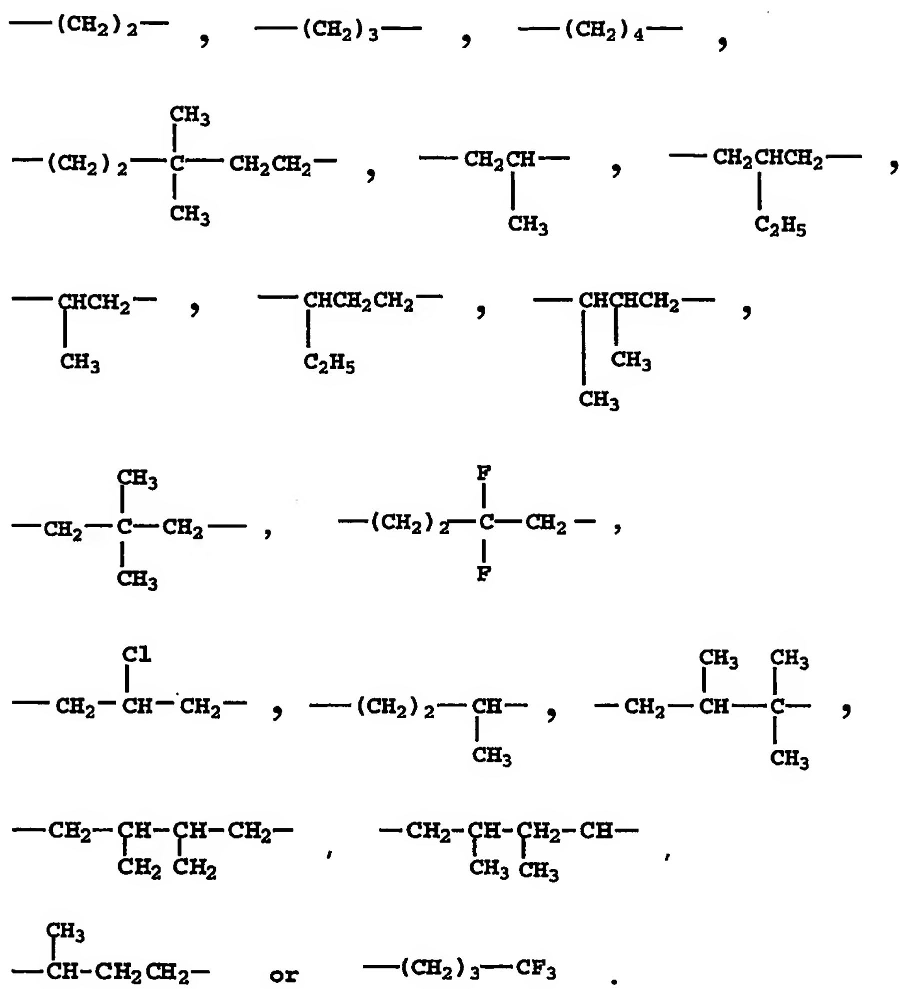
4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, alkylthio or any of the substituents for alkyl as set out herein.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cyclohetero-alkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, or any of the substituents for alkyl as set out herein.

The term "alkylene" as employed herein alone or as part of another group refers to alkyl groups as defined above having single bonds for attachment to other groups at two different carbon atoms and may optionally be substituted as defined above for "alkyl".

The terms "alkenylene" and "alkynylene" as employed herein alone or as part of another group refer to alkenyl groups as defined above and alkynyl groups as defined above, respectively, having single bonds for attachment at two different carbon atoms.

Examples of $(CH_2)_m$, $(CH_2)_n$, $(CH_2)_p$, $(CH_2)_r$, $(CH_2)_s$, $(CH_2)_t$, $CH_2)_u$, $(CH_2)_v$, $(CH_2)_x$, $(CH_2)_y$, $(CH_2)_z$, and other groups (which may include alkylene, alkenylene or alkynylene groups as defined herein, and may optionally include 1, 2, or 3 substituents which may be any of the substituents for alkyl set out herein), are as follows:



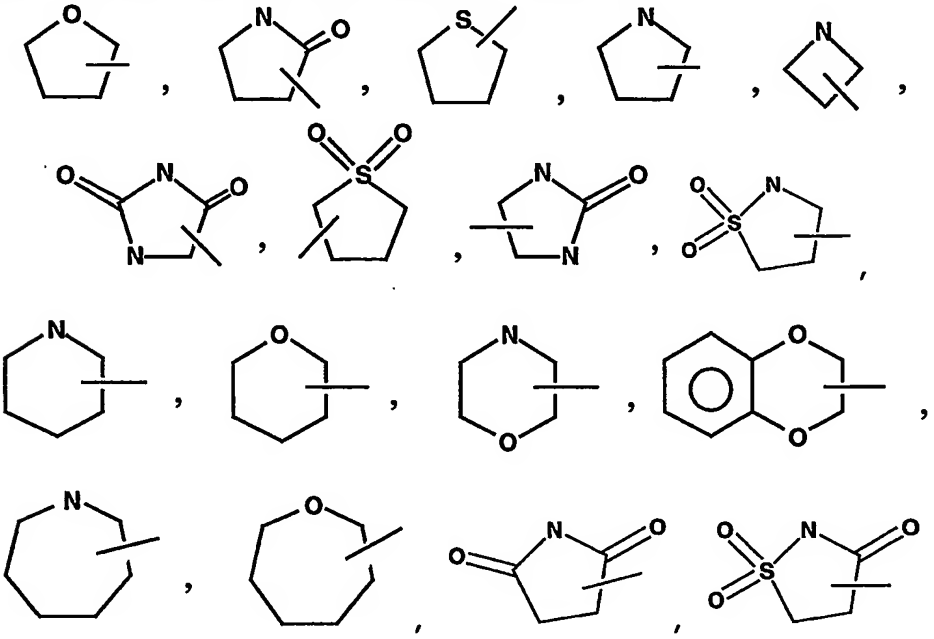
The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or fluorine being preferred.

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

The term "heterocyclic", "heterocyclo" or "heterocycle" as employed herein alone or as part of another group refers to "heteroaryl" groups or "cycloheteroalkyl" groups.

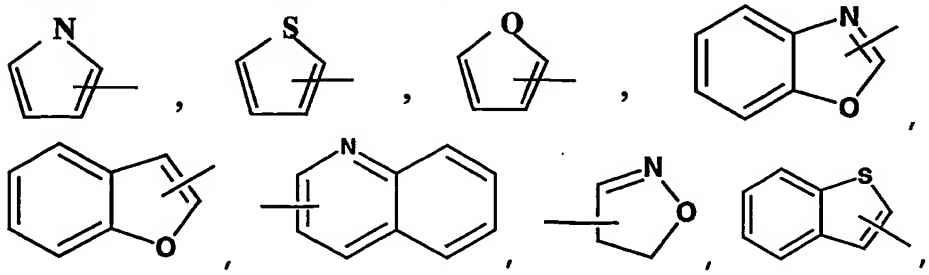
The term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 4-, 5-, 6- or 7-

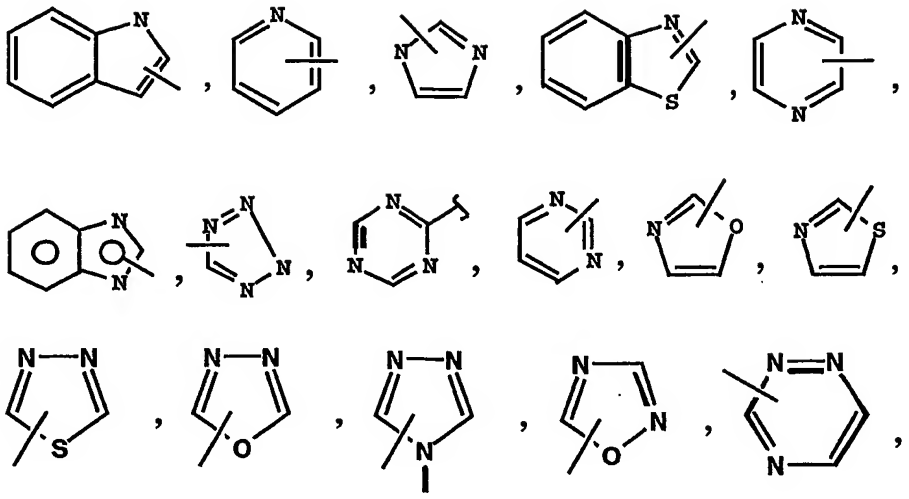
membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as



and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of of the aryl substituents set out herein. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

The term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur,and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides, such as





and the like.

The heteroaryl groups may optionally include 1 to 4 substituents such as any of the aryl substituents set out herein as well as carbonyl and arylcarbonyl. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

Preferred are compounds of formula IB wherein R_1 is alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryl, or heteroarylalkyl, and where these groups may be further optionally substituted with a J1 group;

R_2 is alkyl, aryl, arylalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryl, cycloalkyl, cycloalkylalkyl, or heteroarylalkyl, and these groups may be further optionally substituted by J1a;

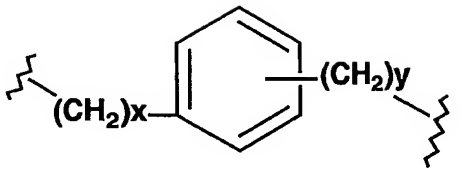
X is -O- or -N-R_4;

R_3 and R_{3a} are the same or different and are independently H, alkoxy, halogen, -CF3;

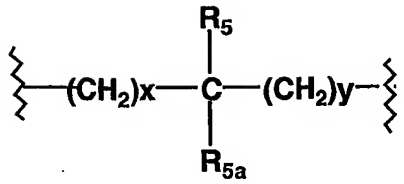
R_4 is H or C_1-C_6 alkyl;

m and n are independently 0 or 1;

Y is



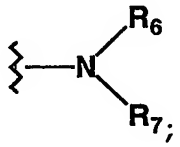
or



where x and y are independently 0 to 3;

R_5 and R_{5a} are the same or different and are independently H, alkyl, $-CF_3$, or R_5 and R_{5a} can be independently joined to one or both of R_6 and R_7 groups (see X_2) to form an alkylene bridge of 1 to 5 carbon atoms;

X_2 is



;

R_6 and R_7 are the same or different and are independently H or alkyl, where alkyl can optionally be substituted with halogen, 1 or 2 hydroxyls, 1 or 2 C_1-C_{10} alkanoyloxy, 1 or 2 C_1-C_6 alkoxy, phenyl, phenoxy, C_1-C_6 alkoxycarbonyl; or R_6 and R_7 can together form $-(CH_2)_tX_5(CH_2)_u-$ where X_5 is $C(R_4)(R_{4a})$ or O, t and u are independently 1-3;

X_3 is $-C(O)-$, $-C(O)O-$, or $-S(O)_2N(R_4)$;

X_4 is a bond, $-O-$, $-OC(O)-$, or $-N(R_4)C(O)-$;

J1 is $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vN(T_{1a})C(O)OT_1$, $-(CH_2)_vN(T_{1a})C(O)N(T_{1b})T_1$, $-(CH_2)_vSO_2T_1$, $-(CH_2)_vN(T_{1a})SO_2T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)N(T_{1a})T_1$, $-(CH_2)_vN(T_{1a})SO_2N(T_{1b})T_1$, $-(CH_2)_vOT_1$, $-(CH_2)_vSO_2N(T_{1a})T_1$, $-(CH_2)_vC(O)T_1$, or heteroaryl, with v being 0-2;

J1a is halogen, $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOT_1$, or $-(CH_2)_vC(O)T_1$, with v being 0-2;

T_1, T_{1a} and T_{1b} are the same or different and are independently H, alkyl, aryl, alkaryl, or cycloalkyl;

each optionally substituted with halogen, hydroxyl or alkoxy; with the proviso that T_1 cannot be hydrogen when it is connected to sulfur as in SO_2T_1;

Most preferred are compounds of the formula IB, wherein R_1 is alkyl, aryl, arylakyl, cycloalkyl, and cycloalkylalkyl and where these groups may be further optionally substituted with a J1 group;

R_2 is alkyl, aryl, arylalkyl, or cycloalkyl, and these groups may be further optionally substituted by J1a;

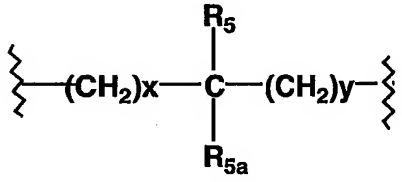
X is -NH or $-NCH_3$;

R_3 and R_{3a} are each H;

m is 1;

n is 0;

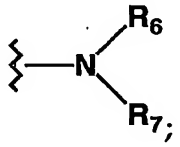
Y is



where x and y are independently 0 or 1, with the proviso that both cannot be 0;

R_5 and R_{5a} are the same or different and are independently H, alkyl, $-CF_3$; or R_5 and R_{5a} can be independently joined to one or both of R_6 and R_7 groups (see X_2) to form an alkylene bridge of 1 to 5 carbon atoms;

X_2 is



R_6 and R_7 are the same or different and are independently H or alkyl where alkyl may be optionally substituted with halogen, or 1 to 2 hydroxyls;

X_3 is $-C(O)-$, $-C(O)O-$, or $-S(O)_2N(R_{4f})$;

X_4 is $-O-$, or $-OC(O)-$;

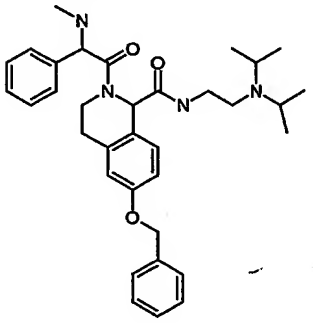
J1 is $-(CH_2)vCN$, $-(CH_2)vN(T_{1a})C(O)T_1$,

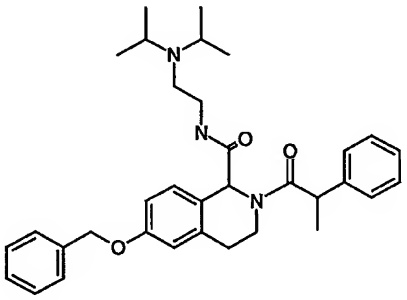
$-(CH_2)_vN(T_{1a})C(O)OT_1$, $-(CH_2)_vN(T_{1a})C(O)N(T_{1b})T_1$, $-(CH_2)_vSO_2T_1$, $-(CH_2)_vN(T_{1a})SO_2T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)N(T_{1a})T1$, $-(CH_2)_vN(T_{1a})SO_2N(T_{1b})T_1$, $-(CH_2)_vOT_1$, $-(CH_2)_vSO_2N(T_{1a})T_1$, $-(CH_2)_vC(O)T_1$, or heteroaryl, with v being 0-2;

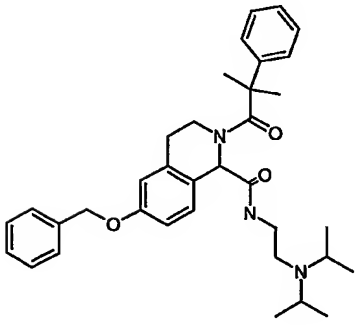
J1a is halogen, $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOT_1$, or $-(CH_2)_vC(O)T_1$, with v being 0-2;

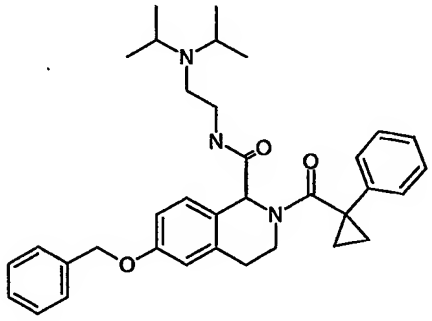
T_1, T_{1a} and T_{1b} are the same or different and are independently H, alkyl, aryl or alkaryl, each optionally substituted with halogen, hydroxyl or alkoxy; with the proviso that T_1 cannot be hydrogen when it is connected to carbonyl or sulfur, as in $C(O)T_1$ or SO_2T_1;

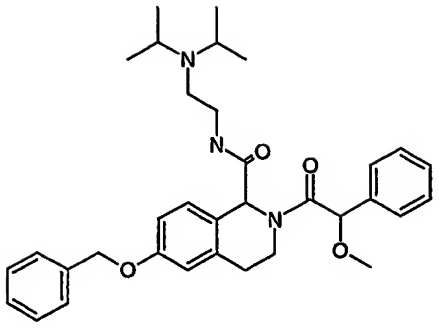
Examples of preferred compounds of the invention include the following:

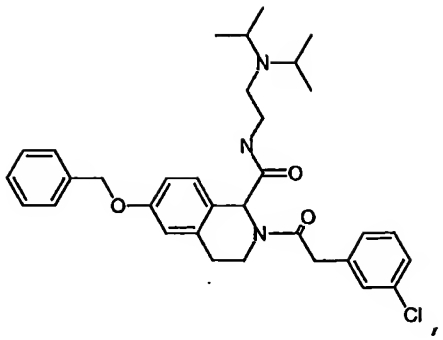












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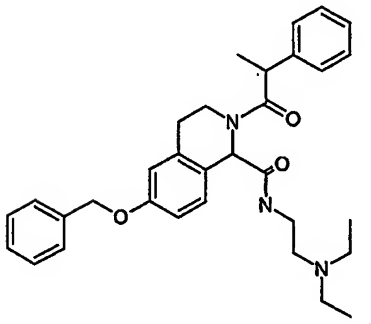

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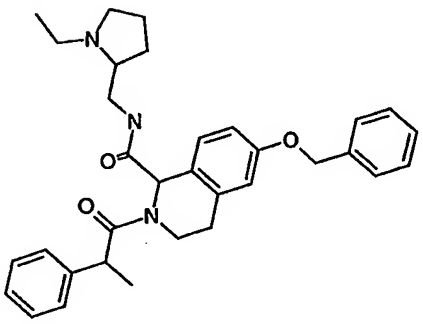
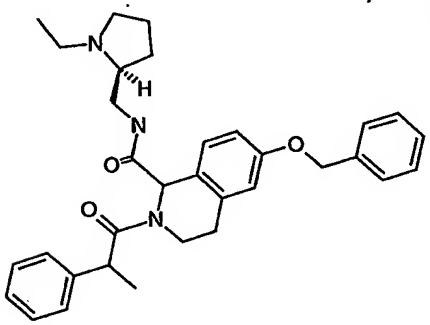
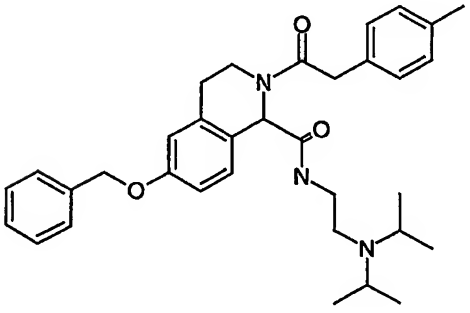


,

Chiral



, and



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5

General Synthetic Schemes

The compounds of the present invention may be prepared according to the following general synthetic schemes, as well as relevant published literature
10 procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions

appear hereinafter and in the working Examples. Unless otherwise specified, the various substituents of the compounds are defined in the same manner as the formula I compound of the invention.

With respect to the following reaction schemes, amide bond forming reactions are conducted under standard peptide coupling procedures know in the art. Optimally, the reaction is conducted in a solvent such as DMF at 0°C to room temperature using EDAC (WSC) (1-ethyl-3-(dimethyl- aminopropyl)carbodiimide), HOBt(1-hydroxybenzotriazole) or HOAt (1-hydroxy-7-aza-benzotriazole) and a base (Hunigs base). Carbamates of formula IE can be formed under standard conditions known in the art from chloroformates, the piperidine amine and a base.

Tetrahydroisoquinolines can be formed as shown in Scheme 1. Suitable cyclization procedures are described in *J. Med. Chem.* , 87, 1821-1825 (1984), *Tet. Lett*, 21, 4819 (1980), *Synthesis*, 824 (1987). Alternative examples are shown in Scheme 8 (*J. Org. Chem.*, 61, 8103-8112 (1996); *Tetrahedron*, 43, 5095 (1987)), Scheme 9 (*Syn. Com.* 23, 473-486 (1993); *J Chem. Soc., Perkin Trans 1*, 2497 (1996); *Tet. Lett.*, 37, 5329 (1996)), and Scheme 10 (*Tetrahedron*, 50, 6193 (1994); *Tet. Lett.*, 34, 5747-5750 (1993); *J Chem Soc, Chem Commun*, 11, 966 (1993)) and Scheme 11. The intermediate A in Scheme 8 can be prepared by suitable methods known in the art, such as in *Tet. Lett*, 37, 5453 (1996) and *Synthesis*, 824 (1987). The protecting group Pc in Scheme 8 can be chiral (formamidine activation Meyers, A. I., *J. Org. Chem.*, 61, 8103-8112 (1990)), imparting chirality to compounds 48-50. The synthesis outlined in Scheme 10 can also lead to chiral induction in intermediates 66-71. Intermediates 49, 50, 61, 71 and 78 in Schemes 8 to 11 can be further transformed by methods disclosed in Schemes 1-7.

Protection and deprotection in the Schemes below may be carried out by procedures generally known in the art.

See, for example, T. W. Greene, Protecting Groups in Organic Synthesis, Second Edition, 1991. P in the Schemes below denotes a nitrogen protecting group, optimally BOC or Cbz. The BOC group can be removed under acidic conditions, optimally HCl or trifluoroacetic acid. The Cbz group can be removed via hydrogenolysis, optimally using a palladium catalyst and hydrogen, or using TMSI. P1 in the Schemes below denotes a phenol protecting group such as BOC (removed by acid or base hydrolysis) or benzyl (removed by hydrogenolysis or TMSI).

Phenol intermediates shown in the General Schemes below may be acylated by methods known in the art to prepare esters and carbamates. The same phenol intermediates may be transformed into anilines by methods known in the art, such as Rossi, *J Org Chem*, 37 (1972). The anilines may be acylated by methods known in the art to prepare amides, ureas, and other derivatives covered by X4. The same phenol intermediates can be transformed to acids, esters or amides through an activated intermediate, such as triflate, by methods known in the art; phenol to acid: Jutand *J Chem Soc.*, 23, 1729-1730 (1992), Wang *Tet. Lett.*, 37, 6661-6664 (1996); to esters: Fretz *Tet. Lett.*, 37, 8475-8478 (1996), Horikawa *Heterocycles*, 40, 1009-1014 (1995) ; to amides: Cacchi *Tet. Lett.*, 27, 3931 (1986); to sulfides: Arould *Tet. Lett.*, 37, 4523-4524 (1996), Percec *J Org Chem*, 60, 6895-6903 (1995), Meier *Angew Chem*, 106, 493-495 (1994), Wong *J Med Chem*, 27, 20 (1984). The resulting sulfides can be oxidized to sulfones and sulfoxides by standard methods known in the art, such as meta-chloroperoxybenzoic acid.

The arylation reaction covered in Scheme 2 can be performed under the coupling conditions in the literature described in Evans et al, *Tet Lett*, 39, 2937-2940 (1998).

Please note that in the following Schemes 1-10 the compounds of formula IB (m=1 and n=0) are shown. However, the schemes are also applicable in preparing all compounds of the formula I invention including compounds

of formulae IA, IC and ID of the invention employing reagents or starting materials analogous to those shown in the schemes as will be apparent to one skilled in the art. In the following schemes R_2 is other than hydrogen.

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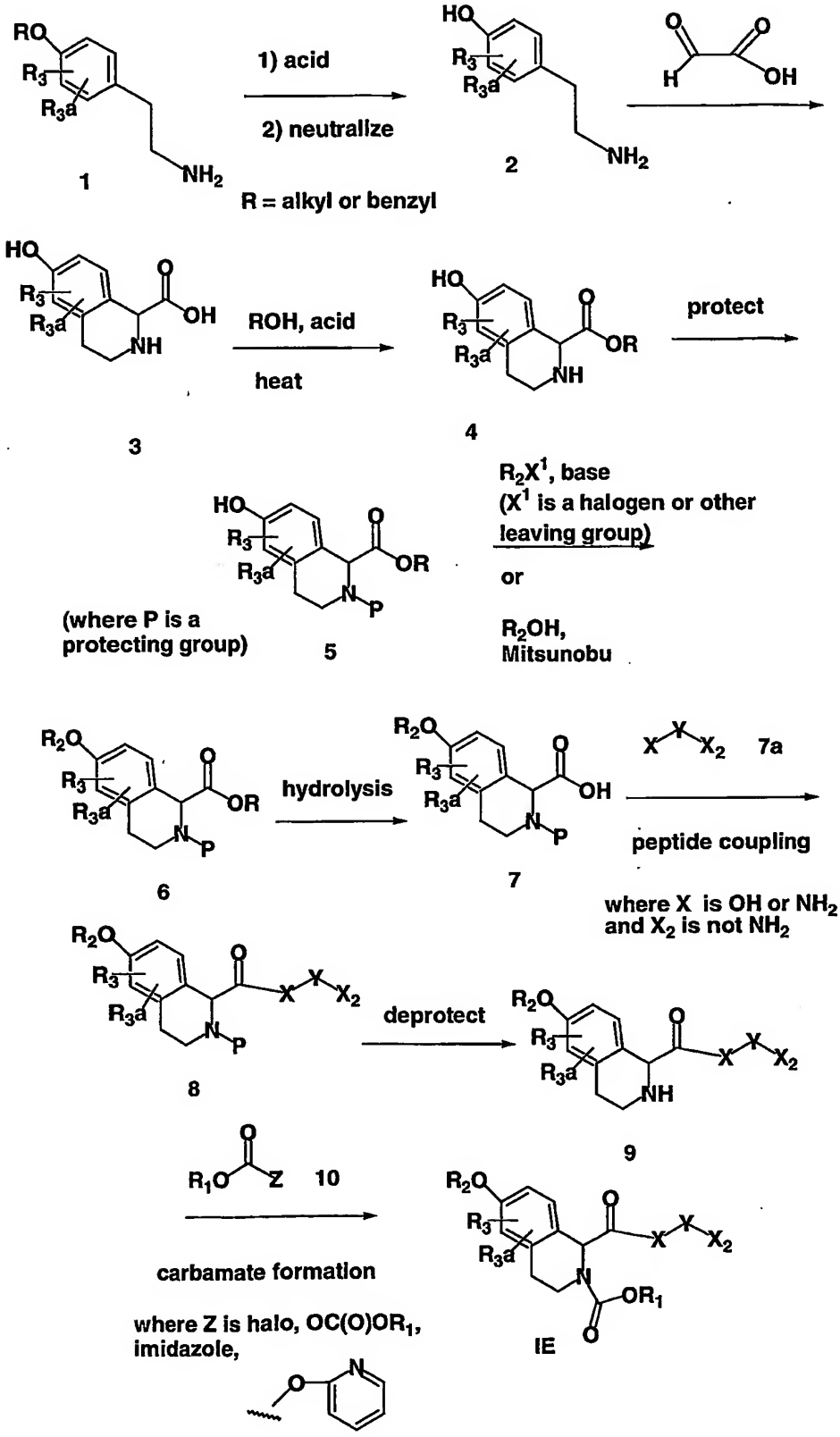
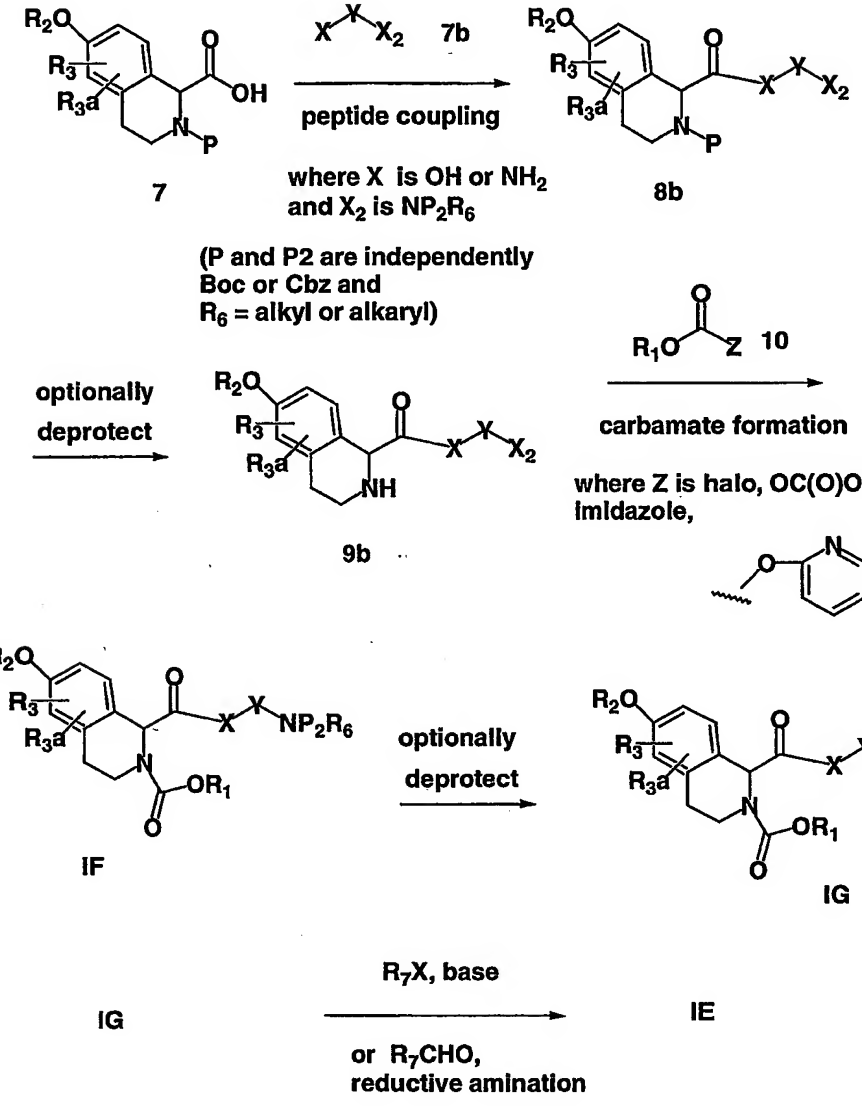
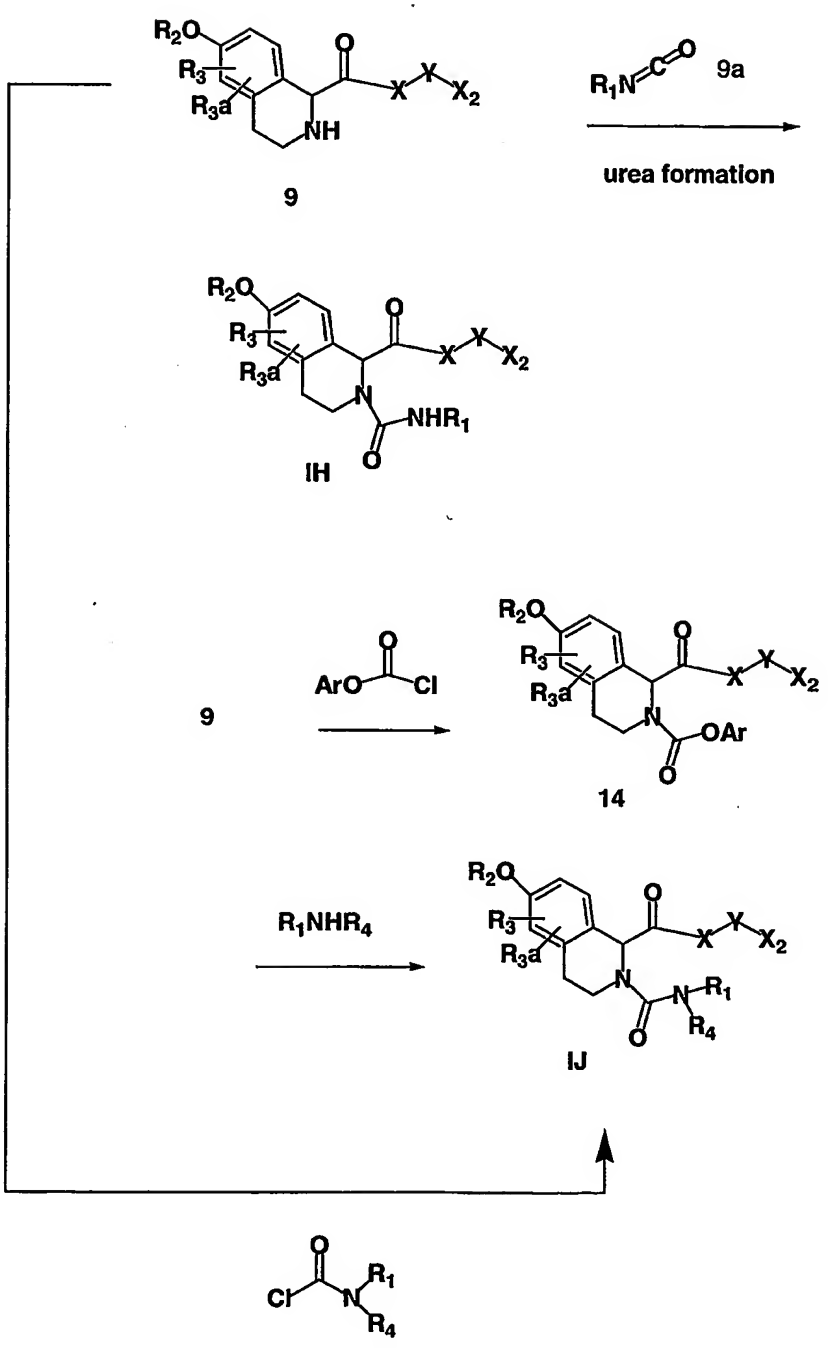
General Scheme 1: Carbamates



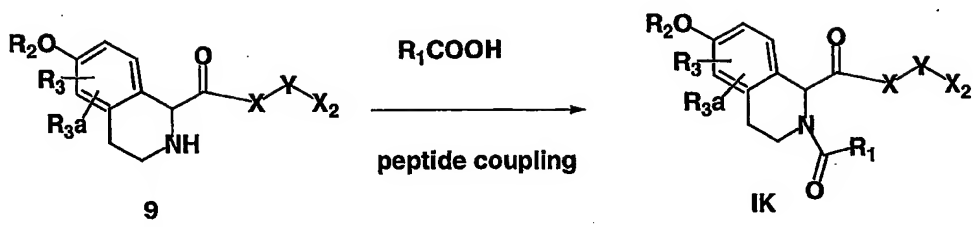
General Scheme 1 alternate: Carbamates



General Scheme 1a: Ureas



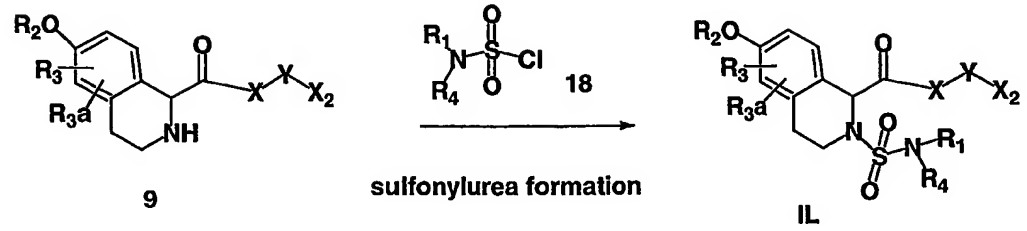
General Scheme 1b: Amides

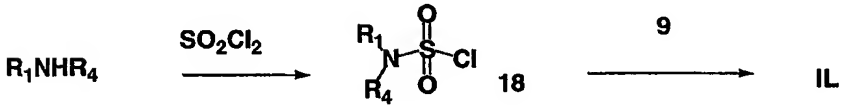


9 IK

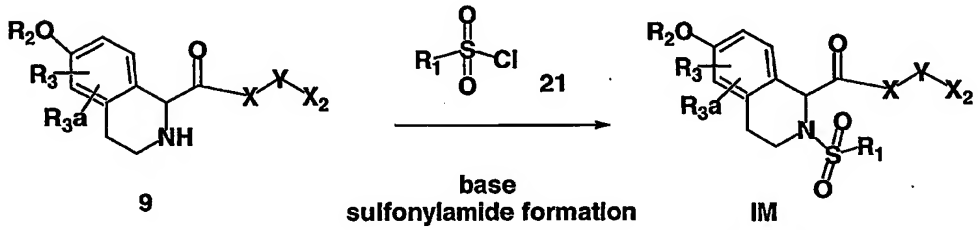
9 IK

General Scheme 1c: SulfonylUreas

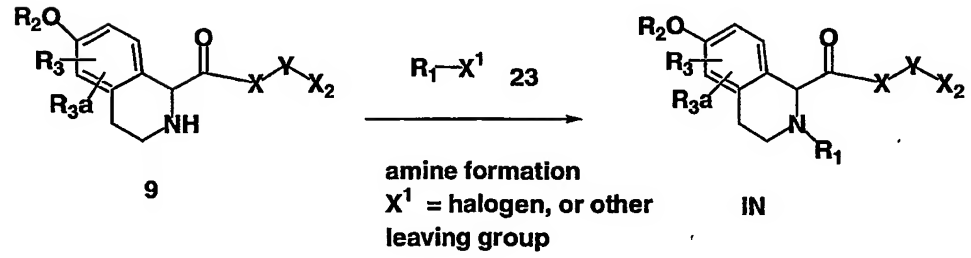




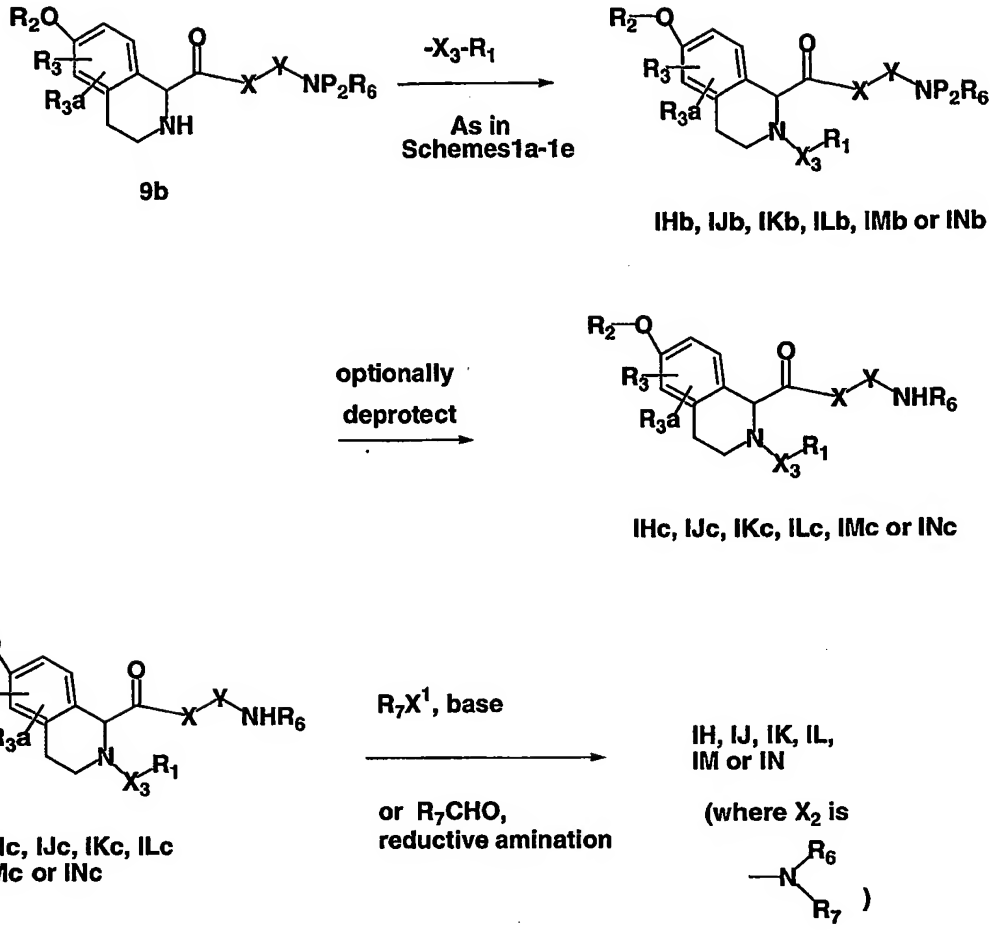
General Scheme 1d: Sulfonylamides



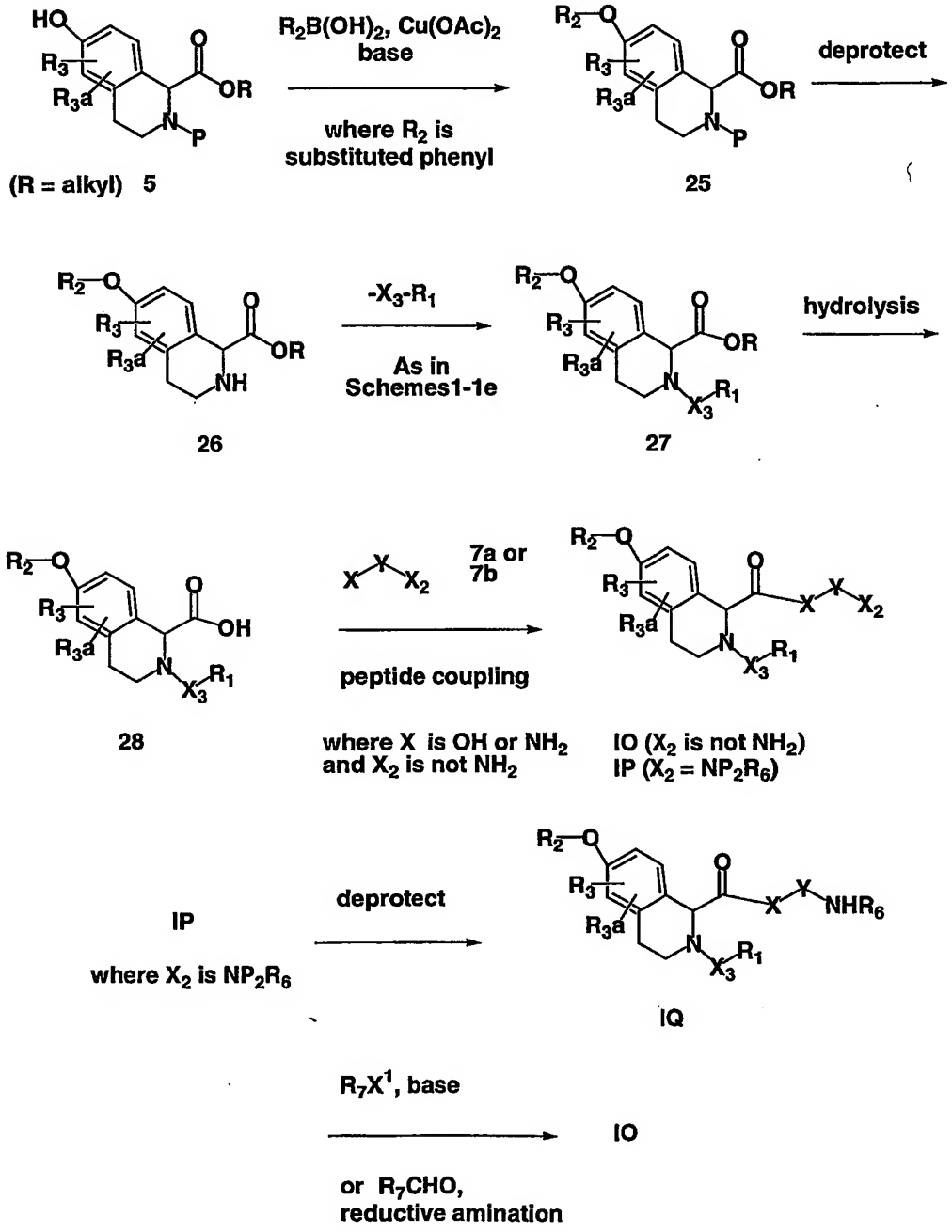
General Scheme 1e: Amines



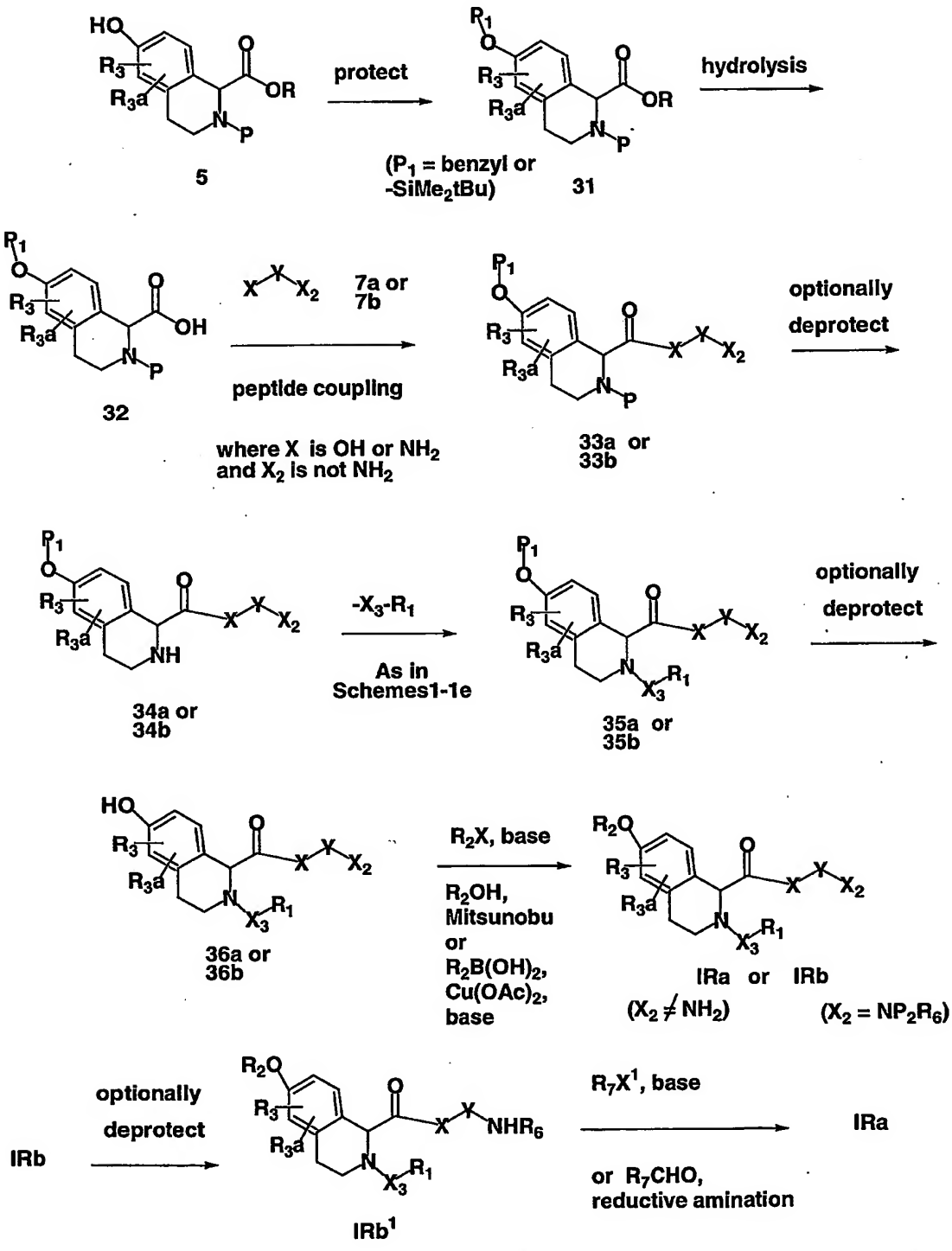
General Scheme 1f



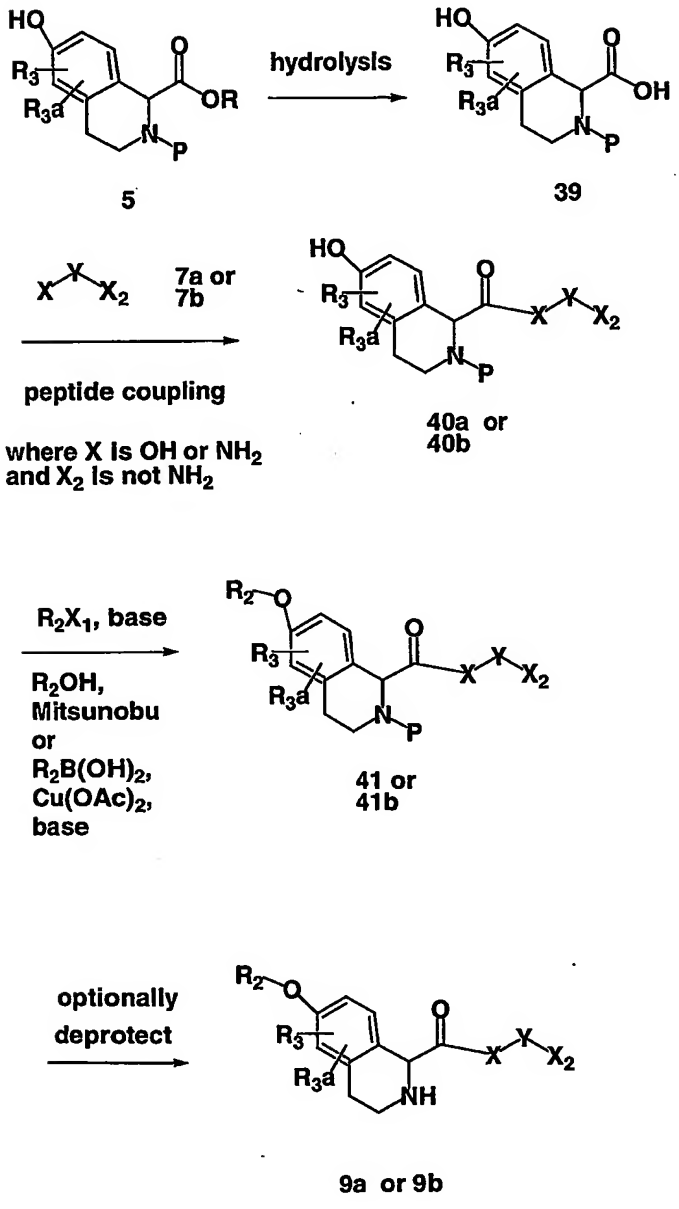
General Scheme 2: Arylation: Where R_2 is Phenyl



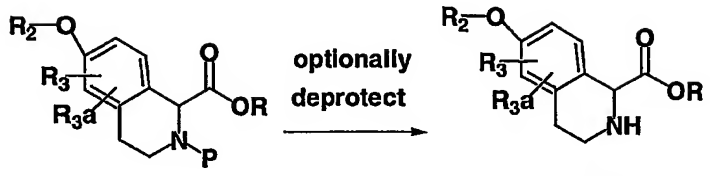
General Scheme 3



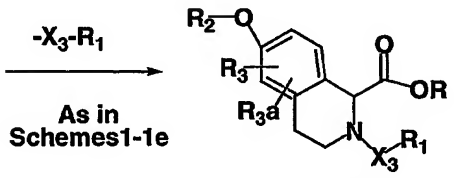
General Scheme 4: Alternate to 9 or 9b



General Scheme 5



6 42



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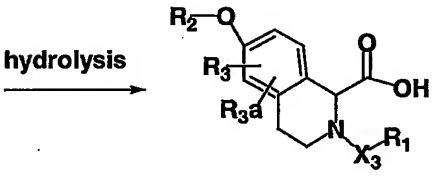

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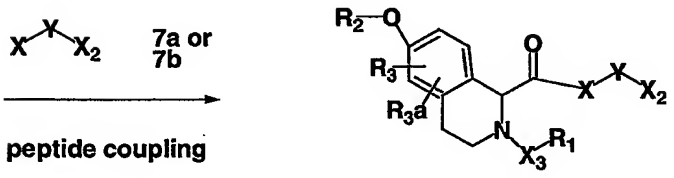
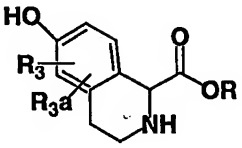


where X is OH or NH_2 and X_2 is not NH_2

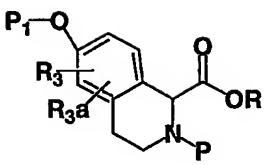
IO or IP

General Scheme 6: Intermediate 39



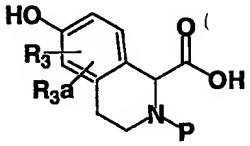
4

protect



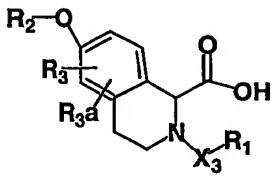
45

hydrolysis

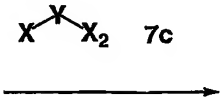


39

General Scheme 7



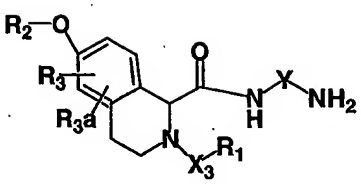
28 or 44



7c

peptide coupling

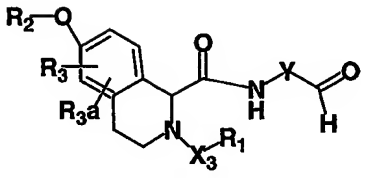
where X and X_2 are NH_2



46

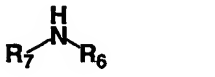
peptide coupling

28 or 44

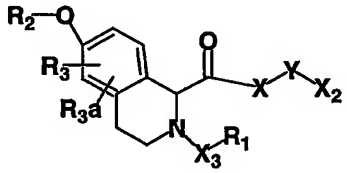


47

methods known
in the art
where X is -OH or $-NH_2$
and
W is an aldehyde or aldehyde precursor
(such as $-CH_2OH$ or $-CH(OMe)_2$)



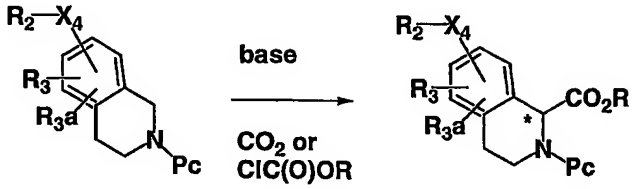
reductive amination



IO or IP

($X_2 \neq NH_2$)

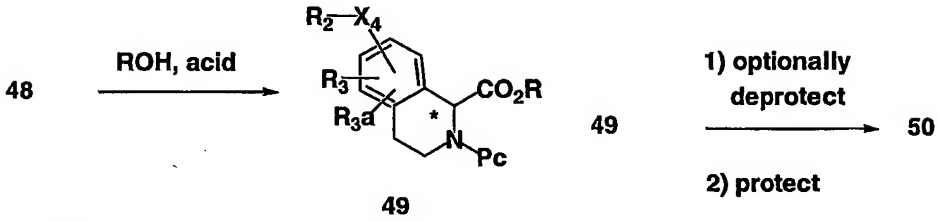
General Scheme 8: Alternate Routes to Core

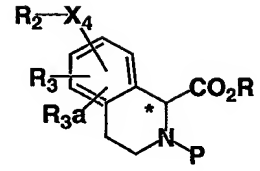


A

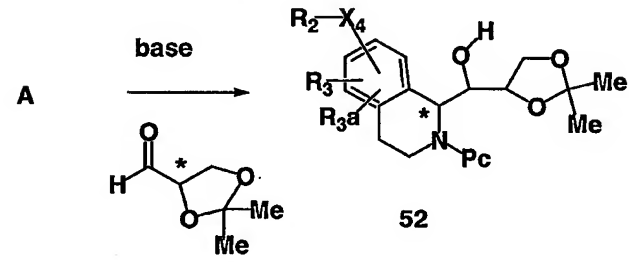
(Pc is a protecting group such as Boc or a chiral imine)

48: R = H
or
49: R = alkyl

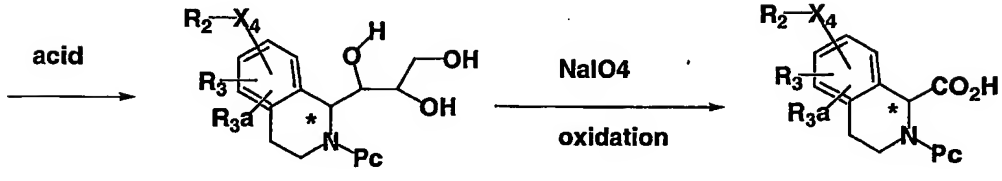




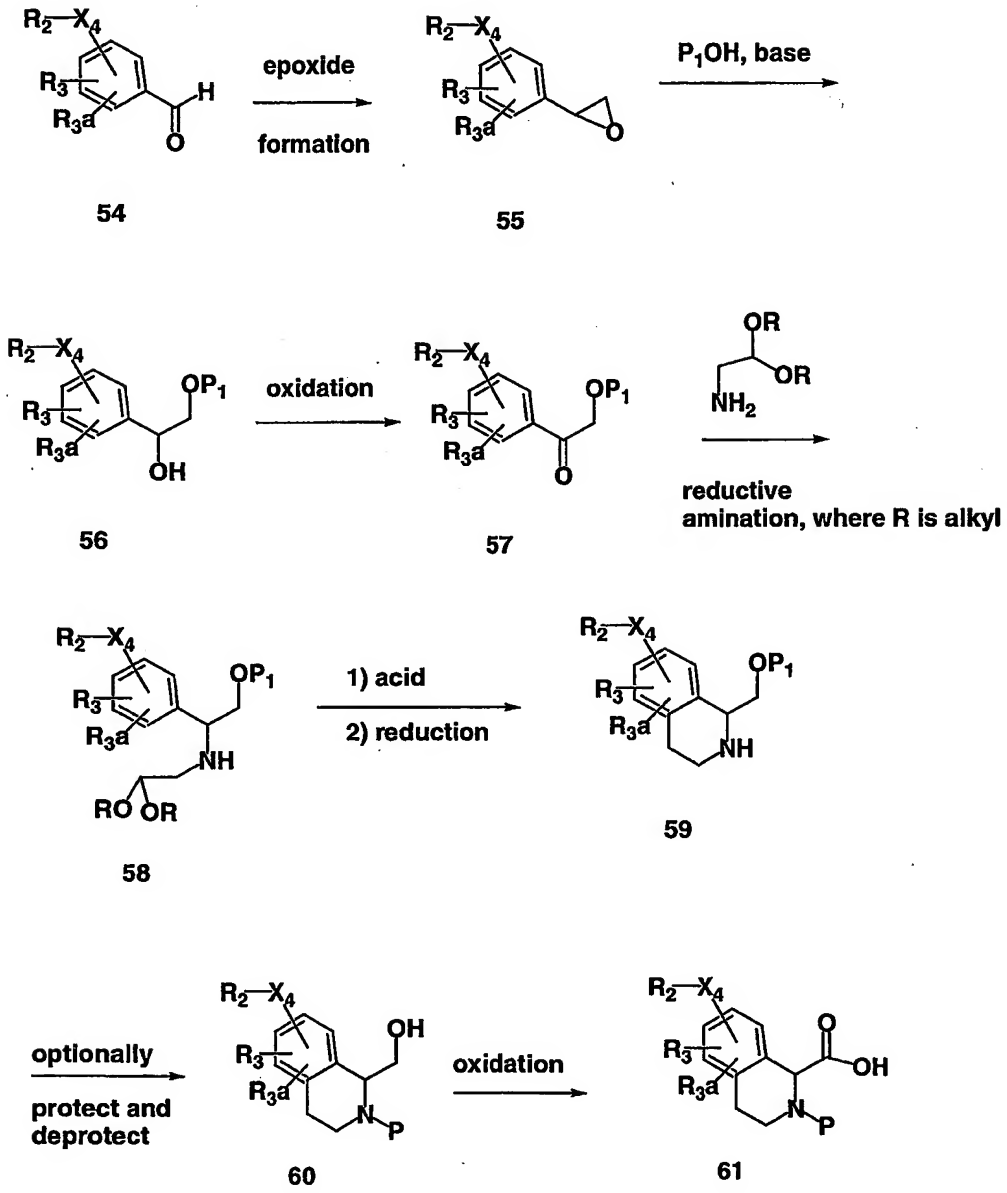
50



51: D, L, or DL

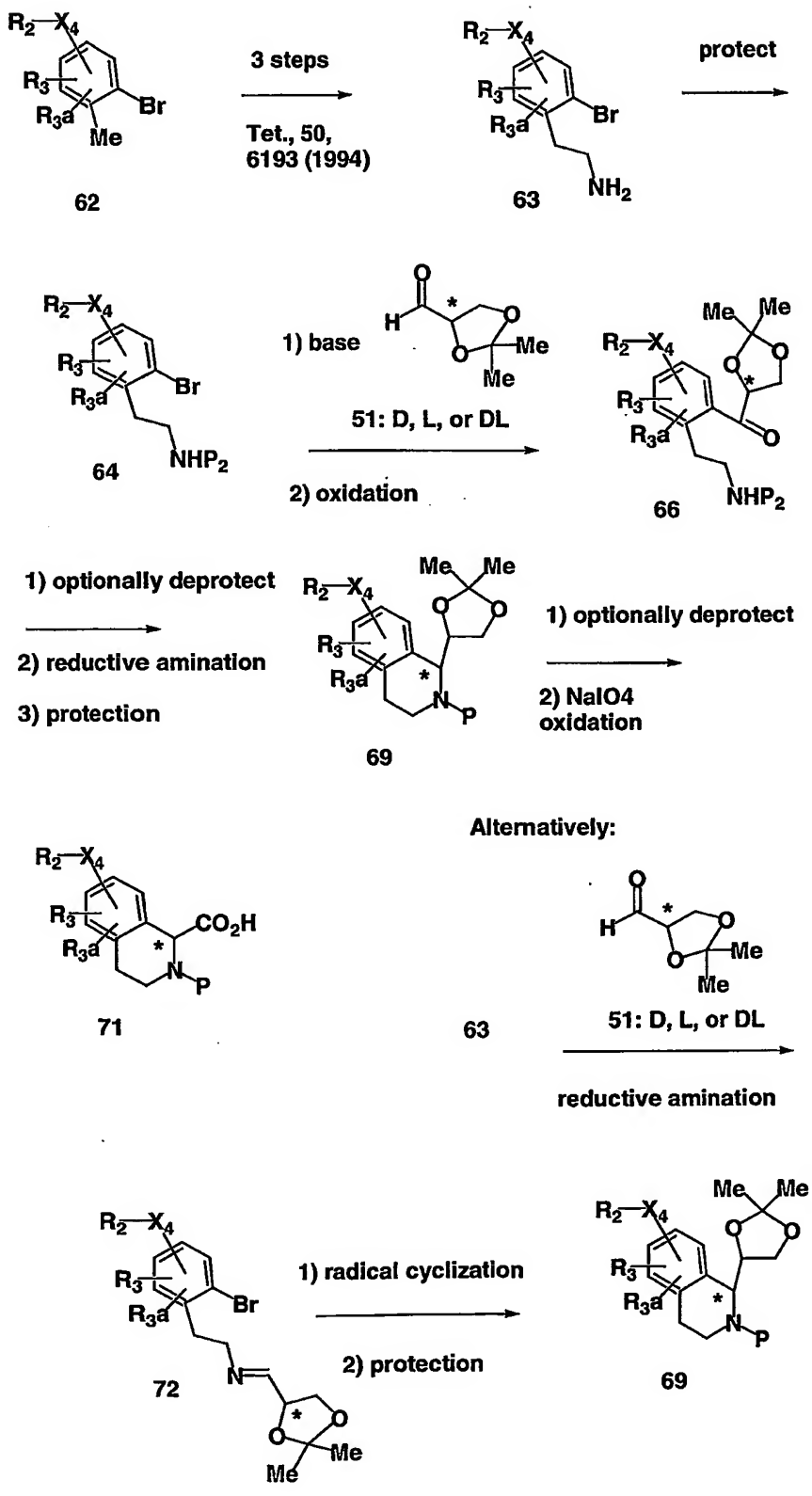


General Scheme 9: Alternate Routes to Core

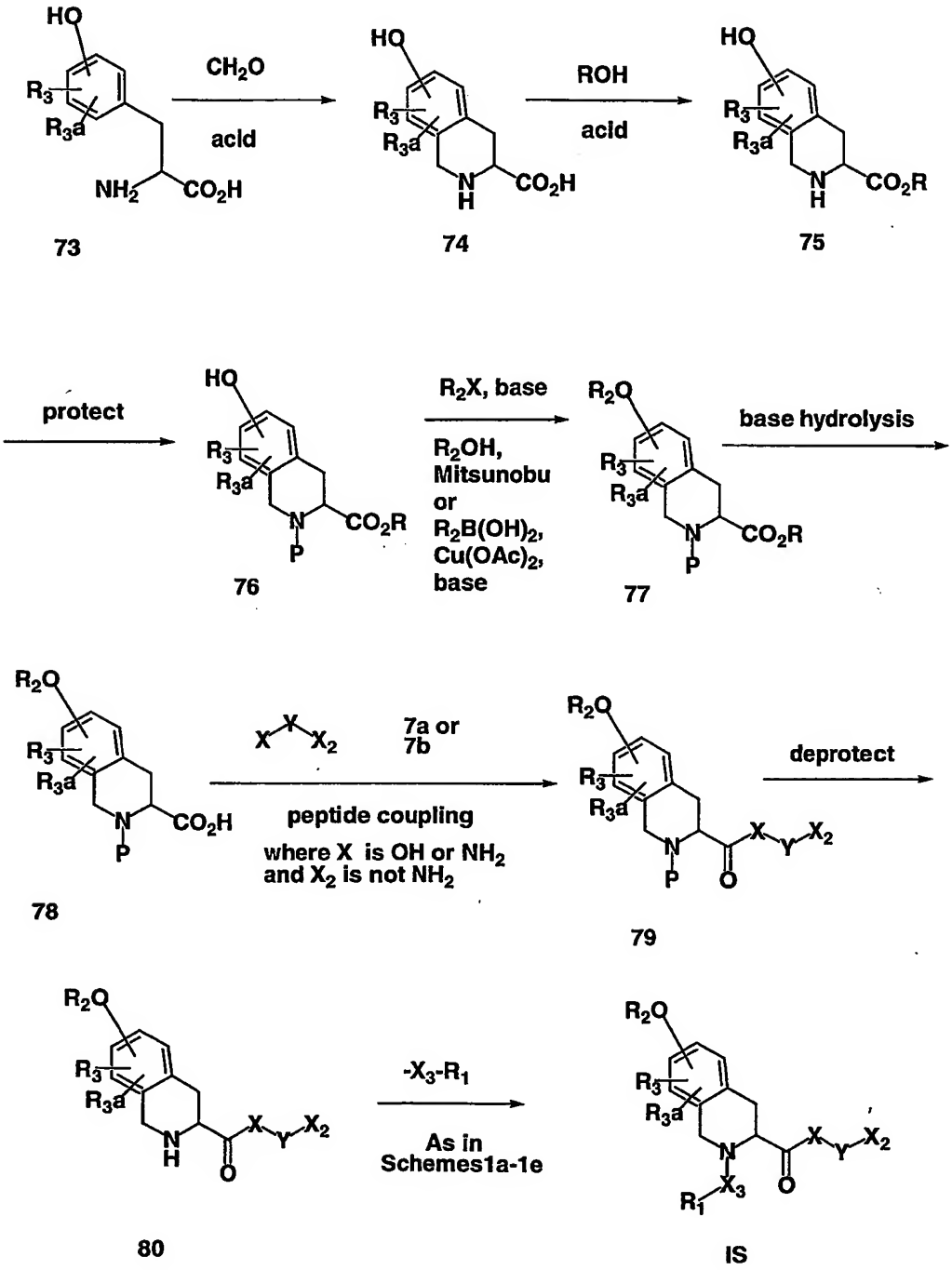


54 55 56 57 58 59 60 61

General Scheme 10: Alternate Routes to Core



Scheme 11: Alternate Core



The chemokine receptor modulator compounds of formula I can be administered to animals, including man, to modulate chemokine receptor activity in vivo.

The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise a growth promoting agent in addition to at least one of the compounds of formula I or another composition which exhibits a different activity, e.g., an antibiotic or other pharmaceutically active material.

The compounds of the present invention are agents that are chemokine receptor modulators and can be administered to various mammalian species, such as monkeys, dogs, cats, rats, humans, etc., in need of treatment. These agents can be administered systemically, such as orally or parenterally.

The compounds of the invention can be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable formulation. The above dosage forms will also include the necessary physiologically acceptable carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral, intranasal or aerosol forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to the age, weight, and condition of the patient, as well as the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms described above may be administered in amounts from about 0.0001 to about 100 mg/kg or body weight or in an amount within the range from about 1 to about 1000 mg per day, preferably, from about 5 to about

500 mg per day in single or divided doses of one to four times daily.

The compounds of the present invention may be employed alone or in combination with each other and/or other chemokine receptor modulators or other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: Anti-diabetic agents; anti-osteoporosous agents; anti-obesity agents; anti-inflammatory agents; anti-anxiety agents; anti-depressants; anti-hypertensive agents; anti-platelet agents; anti-thrombotic and thrombolytic agents; cardiac glycosides; cholesterol/lipid lowering agents; mineralocorticoid receptor antagonists; phospodiesterase inhibitors; protein tyrosine kinase inhibitors; thyroid mimetics (including thyroid receptor antagonists); anabolic agents; HIV or AIDS therapies; therapies useful in the treatment of Alzheimer's disease and other cognitive disorders; therapies useful in the treatment of sleeping disorders; anti-proliferative agents; anti-tumor agents; and/or anti-ulcer and gastroesopheageal reflux disease agents.

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include biguanides (e.g. metformin), glucosidase inhibitors (e.g. acarbose), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g. repaglinide), sulfonylureas (e.g., glimepiride, glyburide and glipizide), biguanide/glyburide combinations (e.g., glucovance), thiozolidinediones (e.g. troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in U.S. Serial No. 09/519,079 filed March 6, 2000 (attorney docket LA27), glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

Examples of suitable anti-osteoporosous agents for use in combination with the compounds of the present invention include alendronate, risedronate, raloxifene, calcitonin, non-steroidal progestin receptor agonists, RANK ligand agonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM), estrogen and AP-1 inhibitors;

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include aP2 inhibitors such as those disclosed in U.S. Serial No. 09/519,079 filed March 6, 2000 (attorney docket LA27), PPAR gamma antagonists, PPAR delta agonists, and orlistat.

Examples of suitable antinflammatory agents for use in combination with the compounds of the present invention include prednisone, dexamethasone, Enbrel, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as NSAIDs, aspirin, indomethacin, ibuprofen, piroxicam, Naproxen, Celebrex, Vioxx), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, integrin antagonists, alpha4 beta7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, tumor necrosis factor (TNF) antagonists (e.g., infliximab, OR1384), prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, and therapies for the treatment of irritable bowel syndrome (e.g., zelmac and Maxi-K openers such as those disclosed in U.S. Patent No. 6,184,231 B1).

Example of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, oxazepam, and hydroxyzine pamoate.

Examples of suitable anti-depressants for use in combination with the compounds of the present invention

include citalopram, fluoxetine, nefazodone, sertraline, and paroxetine.

Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diruetics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

Examples of suitable anti-platelet agents for use in combination with the compounds of the present invention include GPIIb/IIIa blockers (e.g., abciximab, eptifibatide, tirofiban), P2Y12 antagonists (e.g., clopidogrel, ticlopidine, CS-747), thromboxane receptor antagonists (e.g., ifetroban), aspirin, and PDE-III inhibitors (e.g., dipyridamole) with or without aspirin.

Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

Examples of suitable cholesterol/lipid lowering agents for use in combination with the compounds of the present invention include HMG-CoA reductase inhibitors

(e.g., pravastatin lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin)), squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, choesterol absorption inhibitors, and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

Examples of suitable mineralocorticoid receptor antagonists for use in combination with the compounds of the present invention include spironolactone and eplerinone.

Examples of suitable phospodiesterase inhibitiors for use in combination with the compounds of the present invention include PDEIII inhibitors such as cilostazol, and PDE V inhibitors such as sildenafil.

Examples of suitable thyroid mimetics for use in combination with the compounds of the present invention include thyrotropin, polythyroid, KB-130015, and dronedarone.

Examples of suitable anabolic agents for use in combination with the compounds of the present invention include testosterone and SARMs.

Examples of suitable HIV or AIDS therapies for use in combination with the compounds of the present invention include indinavir sulfate, saquinavir, saquinavir mesylate, amprenavir, ritonavir, lopinavir, ritonavir/lopinavir combinations, lamivudine, zidovudine, lamivudine/zidovudine combinations, zalcitabine, didanosine, stavudine, and megestrol acetate.

Examples of suitable therapies for treatment of Alzheimer's disease and cognitive disorders for use in combination with the compounds of the present invention include donepezil, tacrine, revastigmine, 5HT6, gamma secretase inhibitors, beta secretase inhibitors, SK channel blockers, Maxi-K blockers, and KCNQs blockers.

Examples of suitable therapies for treatment of sleeping disorders for use in combination with the compounds of the present invention include melatonin analogs, melatonin receptor antagonists, ML1B agonists, and GABA/NMDA receptor antagonists.

Examples of suitable anti-proliferative agents for use in combination with the compounds of the present invention include cyclosporin A, taxol, FK 506, and adriamycin.

Examples of suitable anti-tumor agents for use in combination with the compounds of the present invention include taxol, adriamycin, epothilones, cisplatin and carboplatin.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

The utility of the compounds of the present invention as chemokine receptor modulators may be demonstrated by methodology known to those skilled in the art, such as the assays for CCR2 and CCR3 ligand binding, as disclosed by Ponath, et al., J. Exp. Med. 1996, 183, 2437-2448, Uguccioni, et al., J. Clin. Invest. 1997, 100, 1137-1143, and White, et al., 2000, J. Biol. Chem. 2000, 275, 36626-36631. Cell lines that express the receptor of interest include those naturally expressing the receptor, or a cell engineered to express a recombinant chemokine receptor, such as CHO, HEK-293, or RBL. The preferred compounds of the present invention have activity in binding to the CCR3 receptor in the aforementioned assays.

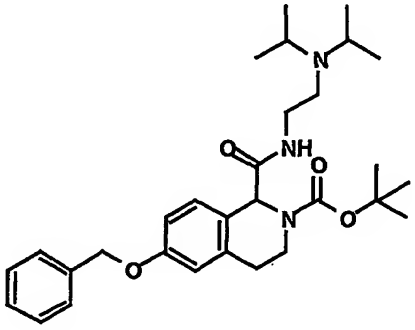
The following Examples represent preferred embodiments of the invention, and are not intended to limit the scope of the claimed invention.

All temperatures are in °C unless indicated otherwise.

General Experimental:

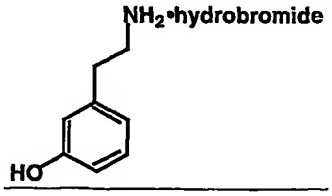
HPLCa: Shimadzu, 0-100% B [MeOH:H_2O:0.2% H_3PO_4], 4 min. gradient, 1 min. hold, 220nM, YMC S5 ODS 4.6 x 50 mm.
HPLCa1: Shimadzu, 0-100% B [MeOH: H_2O:0.2% H_3PO_4], 2 min. gradient, 1 min. hold, 220nM, YMC S5 ODS4.6 x 33 mm.
HPLCb: Shimadzu, 0-100% B [MeOH:H_2O:0.1% TFA], 4 min. gradient, 1 min. hold, 220nM, YMC S5 ODS 4.6 x 50 mm.

Example 1



1-[[[2-[Bis(1-methylethyl)amino]ethyl]amino]carbonyl]-3,4-dihydro-6-(phenylmethoxy)-2(1H)-isoquinoline-carboxylic acid, 1,1-dimethylethyl ester.

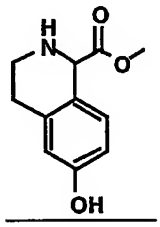
A.



Hydrobromic acid (48%, 500 mL) was added to 3-methoxyphenethylamine (150 g, 0.992 mmol). The formed white solid dissolved upon warming. The reaction mixture was heated at reflux for 3 days. Water was removed by

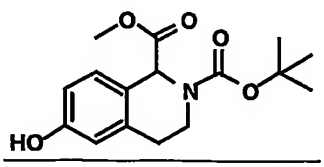
coevaporation with toluene to give the title compound (298 g, >100%) as a white solid%): LC/MS (electrospray, + ions) m/z 138(M+H).

B.



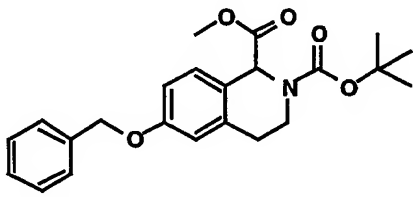
A mixture of Part A compound (266 g, 1.22 mol), glyoxylic acid monohydrate (130 g, 1.41 mol) and 5% hydrochloric acid solution (2 L) was warmed at 80°C under nitrogen for 8 h. Water was removed by azeotroping with toluene. The residue was dissolved in methanol (1500 mL), and then chlorotrimethylsilane (200 mL, 1.58 mol) was added. The suspension became clear after warming to 49°C. Stirring was continued at 49°C for 12 h. The reaction mixture was concentrated, and the residue was treated with saturated aqueous sodium bicarbonate solution to make it basic. The aqueous solution (saturated with sodium chloride) was extracted with ethyl acetate (6 x 300 mL) until no product was visible in the aqueous layer by TLC. Solvent was removed *in vacuo*. Ethanol was added to the residue, and the yellow solid that formed was collected by filtration to give the title compound (87 g, 35%): LC/MS (electrospray, + ions) m/z 208(M+H).

C.



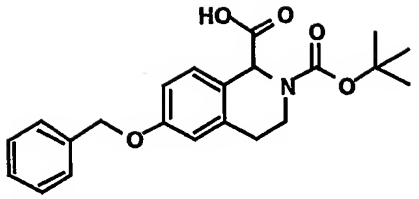
A solution of di-*tert*-butyl dicarbonate (89 g, 0.40 mol) in tetrahydrofuran (500 mL) was slowly added to a suspension of Part B compound (76 g, 0.37 mol) in tetrahydrofuran (800 mL) and triethylamine (5 mL, 0.036 mol). The reaction was stirred at ambient temperature for 2 h until bubbling stopped. The reaction solution was passed through a pad of silica gel, rinsing with tetrahydrofuran. The solvent was removed, and the residue was dissolved in ethyl acetate (400 mL). The ethyl acetate solution was washed with water (500 mL), 10% aqueous citric acid solution (200 mL) and brine. The organic layer was dried over sodium sulfate, and the mixture was filtered. The filtrate was concentrated to give the title compound (128 g, 100%) as a light brown oil: LC/MS (electrospray, + ions) m/z 308(M+H).

D.



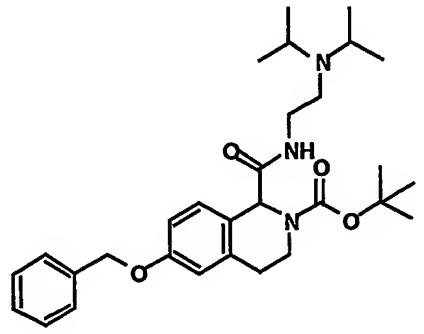
A mixture of Part C compound (48.0 g, 0.156 mol), benzyl bromide (25 mL, 0.209 mol) and potassium carbonate (74 g, 0.536 mol) in dimethylformamide (500 mL) was stirred overnight. The reaction mixture was filtered, rinsing with ethyl acetate, and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, and the organic solution was washed with water followed by 10% aqueous citric acid solution (2x) and brine and then dried over sodium sulfate. The mixture was filtered and the filtrate concentrated. Purification by silica gel column chromatography, eluting with 10% ethyl acetate in heptane (6 L) followed by 20% ethyl acetate in heptane (4 L), gave the title compound (58.0 g, 93%) as a white foam.

E.



Part D compound (21.51 g, 54.12 mmol) was dissolved in methanol (50 mL) and tetrahydrofuran (50 mL), and then water (50 mL) was added. To the resultant milky mixture was added sodium hydroxide (6.49 g, 162.3 mmol). Within 10 min, the reaction temperature rose from 23°C to 40°C, and the reaction became clear. After stirring for 2.5 h, the reaction mixture was transferred to a separatory funnel and water (50 mL) was added. The product was extracted with ethyl acetate (2 x 250 mL). The rich organic layer was washed with 1 N hydrochloric acid solution (250 mL) followed by brine (100 mL) and dried over sodium sulfate. The mixture was filtered, and the filtrate was concentrated and dried *in vacuo* to give the title compound (17.3 g, 83%) as a white foam: LC/MS (electrospray, + ions) m/z 382(M+H).

F.

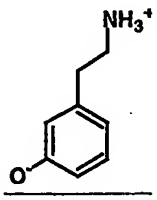


A solution of Part E compound (500 mg, 1.3 mmol) in dimethylformamide (3 mL) was treated with diisopropylethylenediamine (248 µL, 1.37 mmol) followed by 1-hydroxy-7-azabenzotriazole (213 mg, 1.56 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (300 mg, 1.56 mmol). The mixture was stirred overnight at ambient temperature. Evaporation of the solvent gave a residue, which was dissolved in dichloromethane. The dichloromethane solution was washed with water (3 x 30 mL) and dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated. Silica gel flash column chromatography purification gave the title product (523 mg, 79%) as a white solid: LC/MS (electrospray, + ions) m/z 510(M+H).

Example 1A

An alternative procedure for the preparation of Example 1 Part B compound follows:

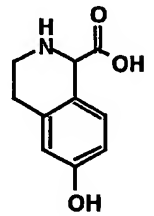
A.



A solution of 48% hydrobromic acid (100 mL) was added slowly and cautiously to a flask at 4°C containing *m*-methoxyphenethylamine (50 g, 0.331 mol). The amine salt formed as a white solid. The reaction mixture was heated at 140°C under gentle reflux for 18 h. After cooling, the solvent was evaporated to give a white residue, which was further dried under high vacuum. The solid was then dissolved in water, and dichloromethane was added to extract the non-polar impurities. The

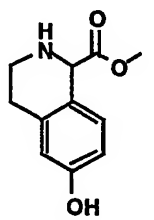
aqueous layer was made alkaline by the addition of powdered sodium carbonate. Water was evaporated to give a white solid, which was dried *in vacuo*. The extraction of the product was done by the addition of ethyl acetate, with heating at reflux. Molecular sieves (4 Å) were added to absorb the residual water. The mixture was decanted. The ethyl acetate extraction was repeated until only trace amounts of product were present in the extract. The ethyl acetate extracts were combined. Ethyl acetate was evaporated to give the title product (29 g, 64%) as a white solid.

B.



To a 4°C solution of Part A compound (3.08 g, 22.5 mmol) in denatured ethanol (70 mL) was added a solution of glyoxylic acid monohydrate (2.0 g, 22 mmol) in ethanol (10 mL) dropwise. Shortly after the addition of glyoxylic acid, a white precipitate formed. The cooling bath was removed, and the reaction mixture was stirred for 2 h at ambient temperature. Filtration gave the title product (3.1 g, 73%) as a white solid: LC/MS (electrospray, + ions) m/z 194(M+H).

C.

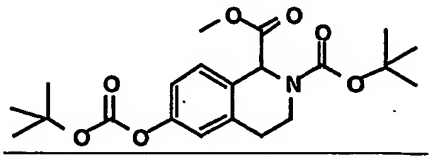


A solution of hydrogen chloride in methanol (150 mL), prepared by the addition of acetyl chloride (13 mL) to methanol (500 mL), was added to Part B compound (6.0 g, 31.1 mmol). The mixture was heated at reflux for 48 h. The solvent was evaporated to give a white residue, to which ethyl acetate and saturated aqueous sodium carbonate were added. The two layers were separated, and extraction of the aqueous layer with ethyl acetate was repeated several times. The ethyl acetate layers were combined and dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated to give the title product (3.93 g, 61%) as a yellow solid: LC/MS (electrospray, + ions) m/z 208(M+H).

Example 1B

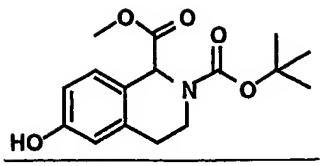
An alternative procedure for the preparation of Example 1 Part C compound follows:

A.



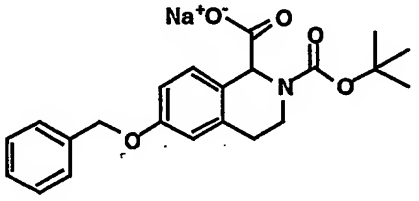
To a mixture of Example 1 Part B compound (3.0 g, 14.5 mmol) and di-*tert*-butyl dicarbonate (8.21 g, 37.6 mmol) was added tetrahydrofuran (75 mL). This mixture was stirred to give a slurry. Triethylamine (5.3 mL, 38.0 mmol) was added, and the reaction mixture was stirred at ambient temperature for 18 h. The title compound was used in the next step without work-up.

B.



To the reaction mixture containing Part A compound was added methanol (30 mL) and then 25 wt% sodium methoxide in methanol (15 mL). The resultant viscous reaction mixture was stirred at ambient temperature for 2 h. A solution of 10% acetic acid in water (50 mL) was added. The reaction temperature rose from 22°C to 34°C, and gas evolution was observed. Tetrahydrofuran and methanol were removed by rotovaporation. The product was extracted with dichloromethane (2 x 50 mL). The organic layer was washed with water (50 mL) and brine (25 mL) and dried over sodium sulfate. The mixture was filtered, and the filtrate was concentrated to give the title product (4.6 g) as a white foam: LC/MS (electrospray, + ions) m/z 308(M+H).

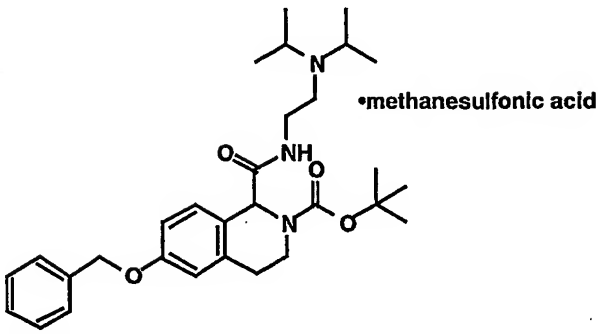
Example 2



To a solution of Part D compound from Example 1 (0.60 g, 1.51 mmol) in tetrahydrofuran (6 mL) was added 1 N sodium hydroxide solution (6 mL, 6 mmol). After stirring for 45 h, the reaction mixture was transferred to a separatory funnel, and the product was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined and washed with 1 N sodium hydroxide solution (5 mL) and brine (5 mL) and then dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was

concentrated and dried *in vacuo* to give the title compound (0.41 g, 67%) as a white solid.

Example 3

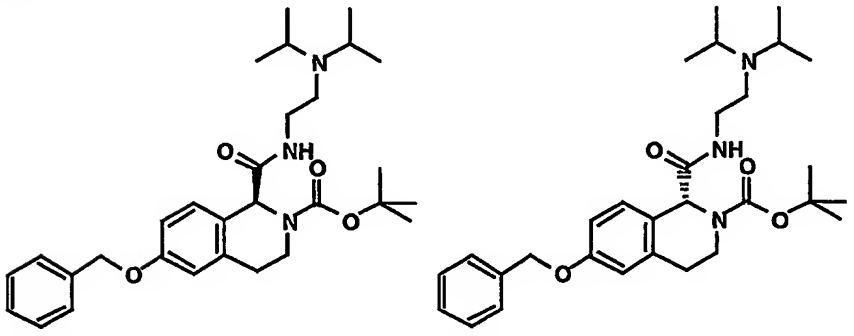


To a solution of Part F compound from Example 1 (107 mg, 0.210 mmol) in dichloromethane (10 mL) was added methanesulfonic acid (16 µL, 0.247 mmol). The solvent was evaporated, and the residue was dissolved in acetone. Hexanes was then added. Concentration gave the title product (110 mg, 86%) as a white solid: LC/MS (electrospray, + ions) m/z 510 (M+H).

Example 4

Isomer A and Isomer B

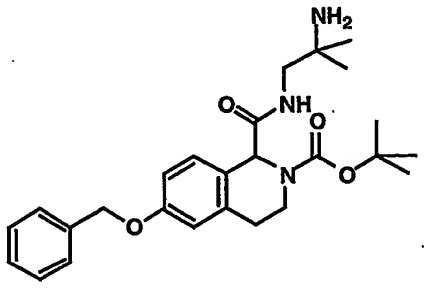
A.



Example 1, title compound (2 batches of 500 mg) was resolved on Chiralpak OD column (50 x 500 mm), eluting with 20% isopropanol in hexanes to give the title compounds, Isomer A (0.350 g, 35%) and Isomer B (0.356 g, 36%).

Isomer A
[α]D = -22.7° (c = 0.1; methanol)
Isomer B
[α]D = +28.4° (c = 0.1; methanol)

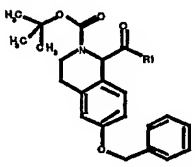
Example 5



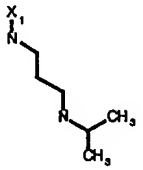
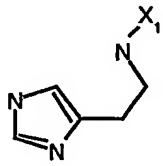
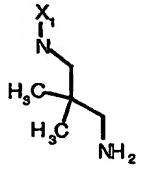
A solution of Part E compound from Example 1 (100 mg, 0.26 mmol) in dimethylformamide was treated with 1,2-diamino-2-methylpropane (27 µL, 0.26 mmol) followed by 1-hydroxy-7-azabenzotriazole (42 mg, 0.31 mmol) and 1,3-diisopropylcarbodiimide (50 µL, 0.32 mmol), and the reaction mixture was stirred overnight at ambient temperature. The crude reaction mixture was loaded onto a SCX column that had been washed with methanol. The column was washed with methanol (3 x 10 mL) and then the product was eluted from the column with 2.0 M ammonia in methanol (6 mL). Evaporation of the solvent gave the title product (109 mg, 92%) as a white solid: LC/MS (electrospray, + ions) m/z 454 (M+H).

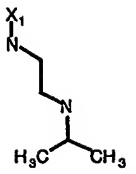
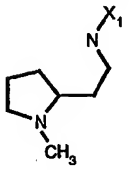
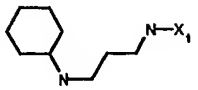
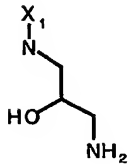
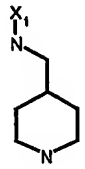
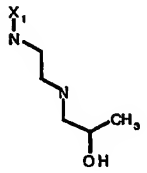
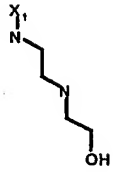
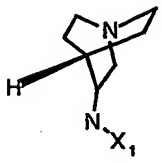
Examples 6 to 26

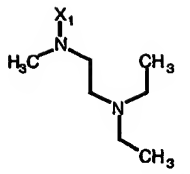
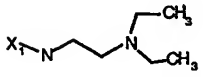
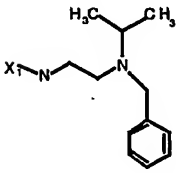
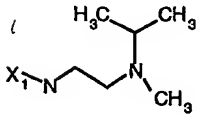
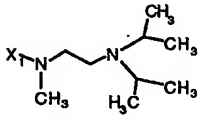
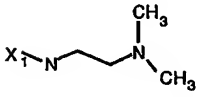
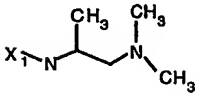
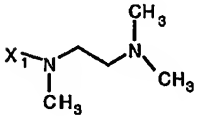
In a manner analogous to that of Example 5, Examples 6-26 listed in the table below were prepared from Part E compound of Example 1 and the respective amines. Examples 6 to 26 compounds were purified by preparative HPLC, eluting with a gradient system of methanol and water with 0.2% trifluoroacetic acid and neutralized with sodium bicarbonate. Example 19-26 compounds were prepared as methanesulfonic acids in a manner analogous to that of Example 3, except that exactly one equivalent of methanesulfonic acid was used. In the tables of compounds which follow, the X_1 designation refers to the point of attachment of the particular R_1 moiety shown to the remainder of the molecule.



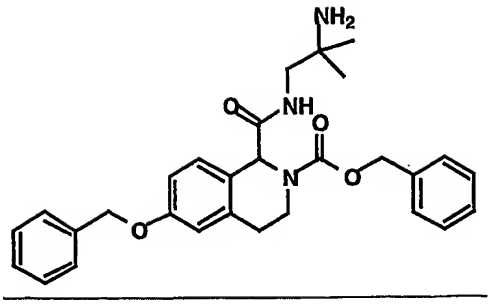
= X_1-R1

Example No.	X_1-R1	LC/MS $(M + H)^+$
6		482
7		477
8		491
9		468

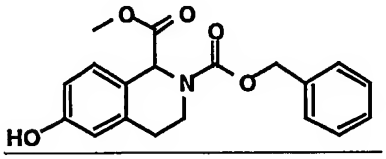
10		468
11		494
12		522
13		456
14		480
15		484
16		470
17		466
18		492

19		496
20		482
21		558
22		482
23		524
24		454
25		468
26		468

Example 27

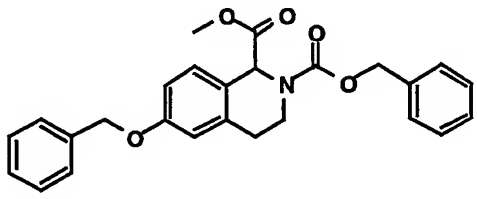


A.



To a suspension of Part B compound from Example 1 (5.0 g, 24 mmol) in dichloromethane (100 mL) was added triethylamine (4.0 mL, 29 mmol). The mixture was cooled to 4 °C and benzyl chloroformate (4.1 mL, 29 mmol) was added dropwise. The reaction mixture became clear and was stirred for 15 min. Additional dichloromethane was added and was washed with water followed by ~5% citric acid solution. The organic layer was dried over magnesium sulfate, and the mixture was filtered. The filtrate was concentrated to give the title compound (8.0 g, 97%) as a yellow solid.

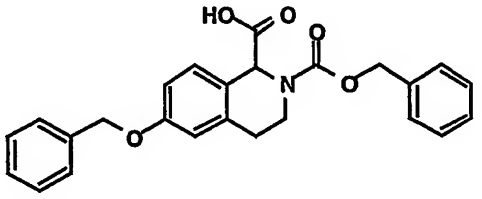
B.



A heterogeneous mixture of Part A compound (8.0 g, 23.5 mmol), benzyl bromide (4.33 g, 23.5 mmol) and potassium carbonate (13 g, 94.1 mmol) in

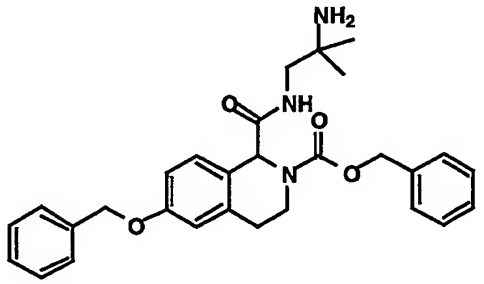
dimethylformamide (20 mL) was stirred at ambient temperature overnight. The reaction mixture was concentrated, and the residue was dissolved in ethyl acetate (300 mL). The organic layer was washed with water (3 x 200 mL) and dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated. Flash column chromatography (1:1 ethyl acetate/hexanes) gave the title product (9.2 g, 91%) as a yellow syrup.

C.



A solution of the methyl ester from Part B compound (3.6 g, 8.38 mmol) in methanol (3 mL) and tetrahydrofuran (3 mL) was treated with 10 M aqueous sodium hydroxide (2 mL, 20 mmol) and stirred at ambient temperature for 2 h. The reaction solution was acidified with 2 N hydrochloric acid solution to pH ~1-2. The product was extracted with ethyl acetate. The organic layer was washed with brine (2x) and dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated to give the title product (3.0 g, 86%) as a yellow solid: LC/MS (electrospray, + ions) m/z 418(M+H).

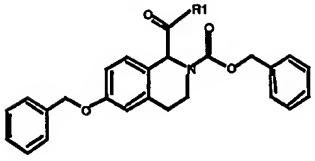
D.



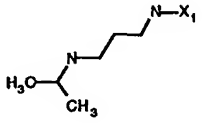
A solution of Part C compound (100 mg, 0.24 mmol) in dimethylformamide (3 mL) was treated with 1,2-diamino-2-methylpropane (30 µL, 0.29 mmol) followed by 1-hydroxy-7-azabenzotriazole (40 mg, 0.29 mmol) and 1,3-diisopropylcarbodiimide (45 µL, 0.29 mmol). The reaction mixture was stirred at ambient temperature overnight. The solvent was removed, and the residue was dissolved in methanol. This solution was applied to a CUBC x 12M6 column, which was prewashed with methanol (10 mL). The column was washed with methanol (3 x 10 mL), and then the product was eluted with 2 M ammonium in methanol (10 mL). Evaporation of the solvent gave the title compound (110 mg, 94%) as a white solid: LC/MS (electrospray, + ions) m/z 488 (M+H).

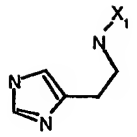
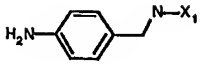
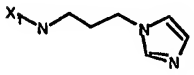
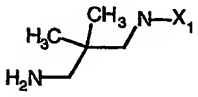
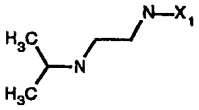
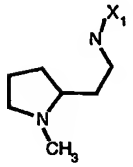
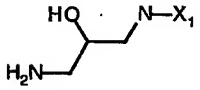
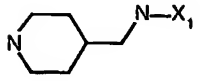
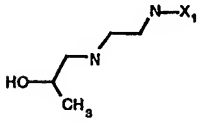
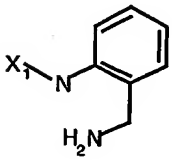
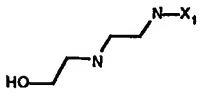
Examples 28 to 45

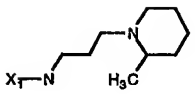
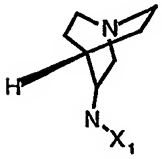
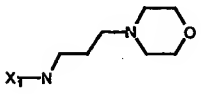
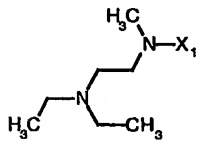
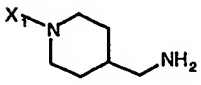
In a manner analogous to that of Example 27, Examples 28-45 listed in the table below were prepared from Part C compound of Example 27 and the respective amines. Examples 38 and 45 compounds were purified by preparative HPLC, eluting with a gradient system of methanol and water with 0.2% trifluoroacetic acid. These compounds were isolated as trifluoroacetic acid salts.



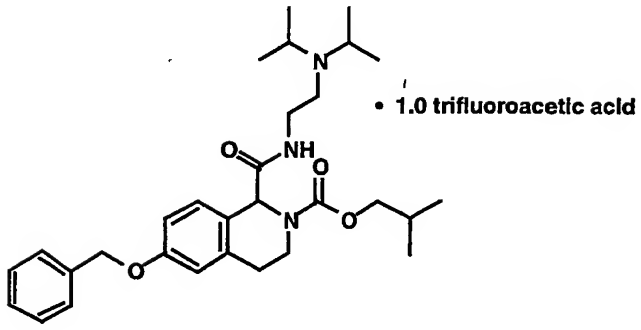
= X_1-R1

Example No.	X_1-R1	LC/MS $(M + H)^+$
28		516

29		511
30		522
31		525
32		502
33		502
34		528
35		490
36		514
37		518
38		522
39		504

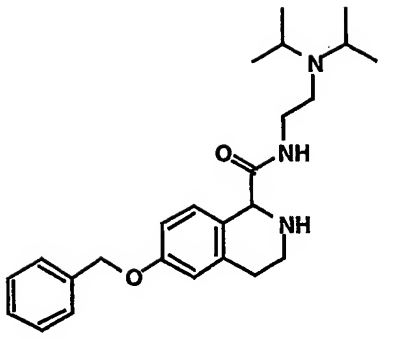
40		500
41		556
42		526
43		544
44		530
45		514

Example 46



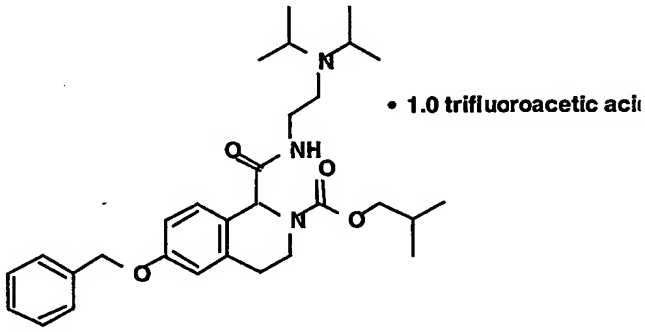
5

A.



To a flask containing Example 1, title compound, (1.57 g, 3.1 mol) was slowly added 4 N hydrogen chloride in dioxane (10 mL, 40 mol) with a syringe at ambient temperature. It was stirred for 1 h and then concentrated. The residue was dissolved in ethyl acetate and then the pH was adjusted to ~pH 8 with the addition of 1 N sodium hydroxide solution. The ethyl acetate layer was separated and dried over sodium sulfate. The mixture was filtered and the filtrate concentrated to give the title compound (1.13 g, 89%) as a yellow oil: LC/MS (electrospray, + ions) m/z 410(M+H).

B.

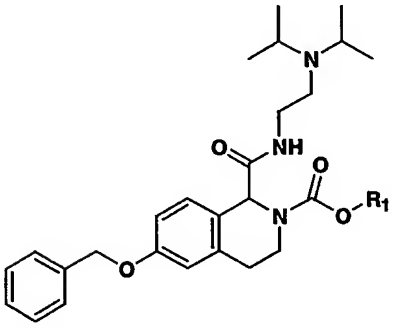


To a 4°C solution of Part A compound (60.0 mg, 0.147 mmol) and triethylamine (30 µL, 0.215 mmol) in tetrahydrofuran (10 mL) was added isobutyl chloroformate (28.5 µL, 0.220 mmol). The mixture was stirred at 0°C to 10°C for 1 h. The mixture was concentrated, and the

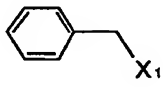
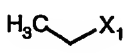
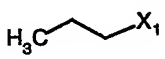
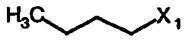
concentrate was purified by preparative HPLC, eluting with a gradient system of 30-100% B (where A = 90% water, 10% methanol, 0.2% trifluoroacetic acid and B = 90% methanol, 10% water, 0.2% trifluoroacetic acid), to give the title compound (81 mg, 89%) as a yellow oil:HPLCa rt = 3.99 min; LC/MS (electrospray, + ions) m/z 510(M+H).

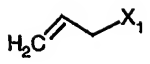
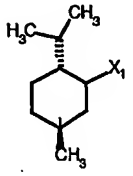
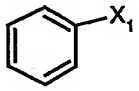
Example 47 to 54

In a manner analogous to that of Example 46, Examples 47-54 compounds listed in the table below were prepared from Part A compound from Example 46 and the respective chloroformate.

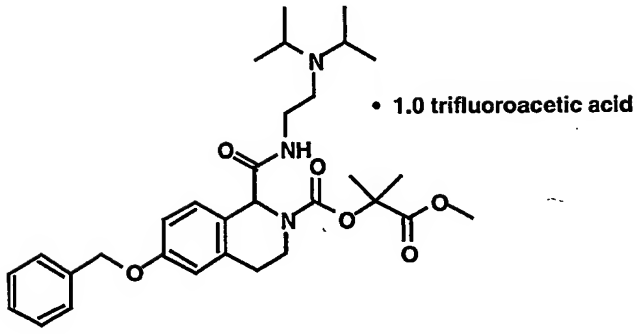


= X_1-R1

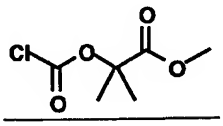
Example No.	X_1-R1	LC/MS (M + H)+
47		544
48		468
49		482
50		496
51		510

52		494
53		592
54		530

Example 55

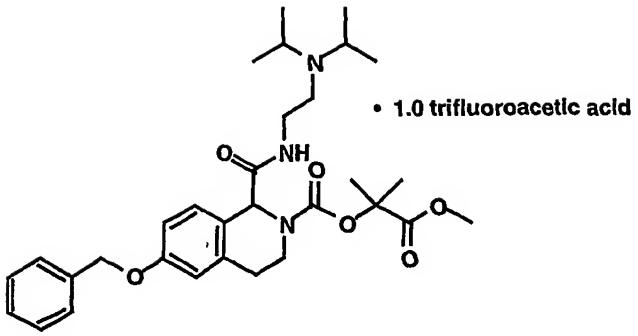


A.



To a -5°C solution of methyl 2-hydroxyisobutyrate (118 mg, 1.0 mmol) and triethylamine (139 µL, 1.0 mmol) in dichloromethane (4 mL) was added 1.9 M phosgene in toluene (0.8 mL, 1.5 mmol). After stirring for 1 h between -5 to 0°C, the reaction mixture was concentrated and used in the next procedure without purification.

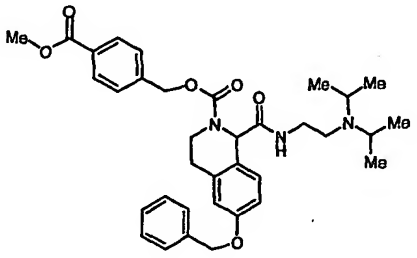
B.

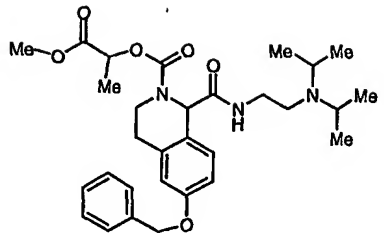
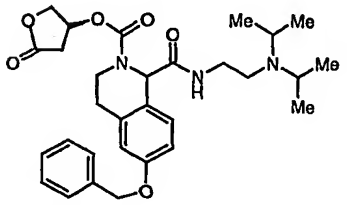
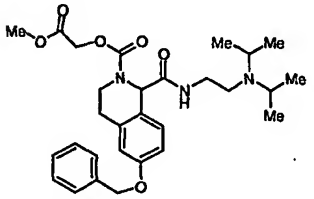
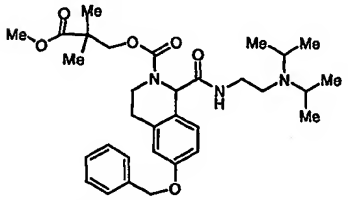
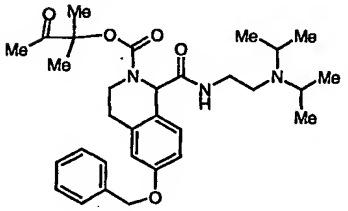
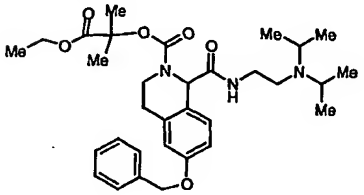


At 0°C, a solution of Part A compound (1.0 mmol) in dichloromethane (5 mL) was treated with Part A compound from Example 46 (45 mg, 0.11 mmol) followed by triethylamine (111 µL, 0.80 mmol). The reaction mixture was stirred at 0°C to 5°C for 2 h and then concentrated. Purification by preparative HPLC, eluting with a gradient system of 30-100% B (where A = 90% water, 10% methanol, 0.2% trifluoroacetic acid and B = 90% methanol, 10% water, 0.2% trifluoroacetic acid), gave the title compound (52.2 mg, 71%) as a yellow oil: HPLCa rt = 3.81 min; LC/MS (electrospray, + ions) m/z 554(M+H).

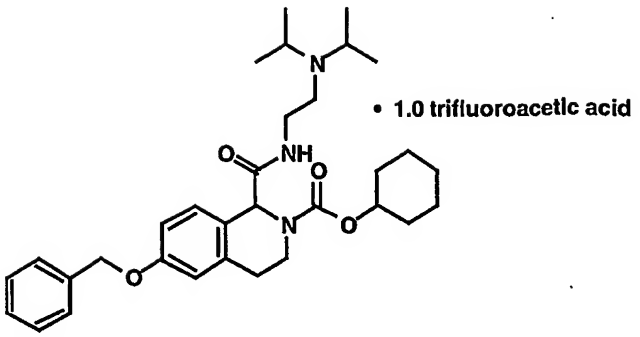
Examples 56 to 62

In a manner analogous to that of Example 55, Examples 56-62 compounds listed in the table below were prepared from Part A compound from Example 46 and the respective chloroformate prepared as in Example 55 Part A.

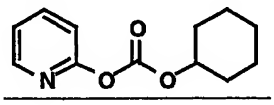
Example No.	Structure	LC/MS (M + H)+
56		602

57		540
58		538
59		526
60		568
61		538
62		568

Example 63

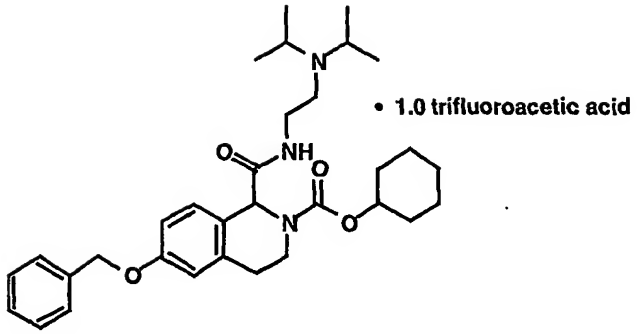


A.



A mixture of cyclohexanol (12.5 µL, 0.12 mmol), carbonic acid di-2-pyridyl ester (25.9 mg, 0.12 mmol) and triethylamine (16.7 µL, 0.12 mmol) in dichloromethane (5 mL) was stirred at ambient temperature overnight. The reaction mixture was concentrated, and the residue was partitioned between ethyl acetate (20 mL) and concentrated sodium carbonate solution. The two layers were separated, and the organic layer was washed with brine and dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated. The title product was purified by silica gel preparative TLC, eluting with 1:1 dichloromethane/ethyl acetate, and isolated in a yield of 26 mg (98%).

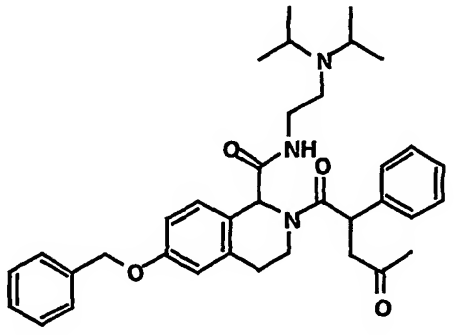
B.



To a solution of Part A compound from Example 46 (81.8 mg, 0.20 mmol) and triethylamine (27.8 µL, 0.20 mmol) in dichloromethane (7 mL) was added Part A compound (26 mg, 0.12 mmol). The reaction mixture was stirred at ambient temperature under nitrogen for 12 h. The mixture was purified by a SCX column as follows. The column was conditioned by rinsing with methanol (10 mL). The reaction mixture was loaded onto the column, followed by methanol (2 x 20 mL) and finally, the product was eluted with 2 N ammonia in methanol (6 mL). Further purification by preparative HPLC, eluting with 30-100% B (where A = 90% water, 10% methanol, 0.2% trifluoroacetic acid and B = 90% methanol, 10% water, 0.2% trifluoroacetic acid), gave the title compound (49.7 mg, 65%) as a yellow oil: LC/MS (electrospray, + ions) m/z 536(M+H).

Example 64

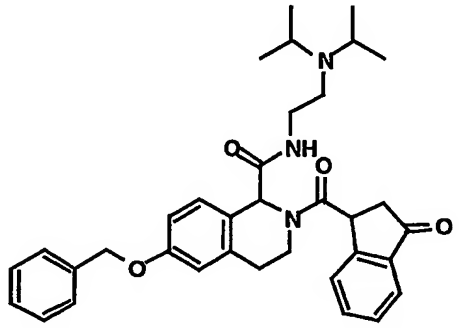
Isomer A and Isomer B



A solution of Part A compound from Example 46 (41.0 mg, 0.1 mmol) in dichloromethane (0.5 mL) was added to 2-phenyllevulinic acid (57.7 mg, 0.3 mmol) in a test tube. To the resultant mixture was added a solution of 1-hydroxybenzotriazole hydrate (33.8 mg, 0.25 mmol) in tetrahydrofuran (0.75 mL) followed by 1,3-diisopropylcarbodiimide (31.6 mg, 0.25 mmol). The reaction was stirred overnight. Methanol (3 mL) was added to ensure the reaction mixture was homogeneous. The mixture was purified by a SCX column as follows. The column was conditioned by rinsing with methanol (10 mL) and then pushing through air (10 mL). The reaction mixture was loaded onto the column. Air (10 mL) was pushed through the column followed by methanol (2 x 20 mL) and air (10 mL). Finally, the product was eluted with 2 N ammonia in methanol (6 mL) followed by air (10 mL). The solvent was removed from the sample by the use of a speed vacuum to give the two isomers of the title compound (56.5 mg, 97%) as an oil: HPLCb rt = 3.73 and 3.92 LC/MS (electrospray, + ions) m/z 584(M+H).

Example 65

Isomer A and Isomer B

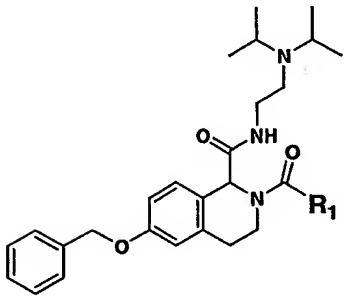


In a manner analogous to that of Example 64, the two isomers of the title compound were prepared from Part A compound from Example 46 (41.0 mg, 0.1 mmol) and 3-oxo-1-indancarboxylic acid (52.9 mg, 0.3 mmol) in yield of

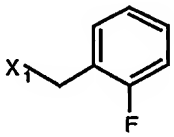
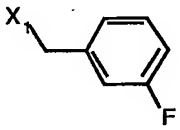
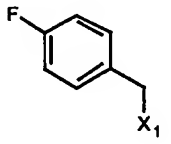
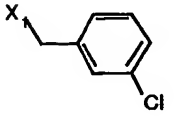
55.2 mg (97%) as an oil: HPLCb rt = 3.45 and 3.51 min; LC/MS (electrospray, + ions) m/z 568(M+H).

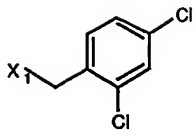
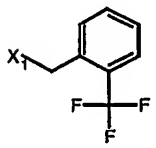
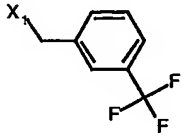
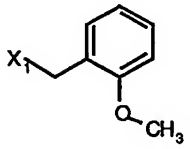
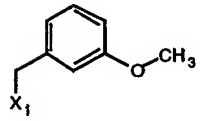
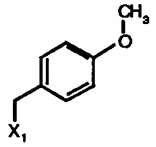
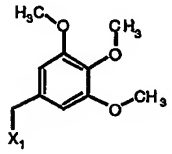
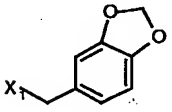
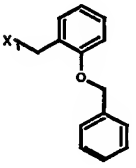
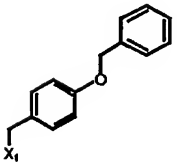
Examples 66 to 200

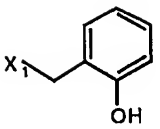
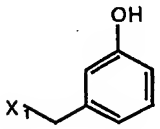
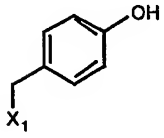
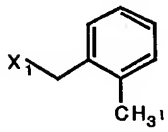
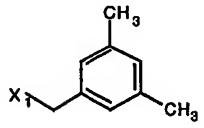
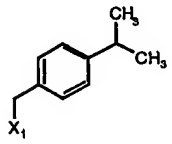
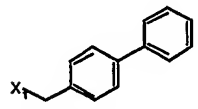
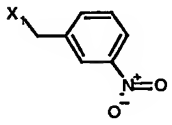
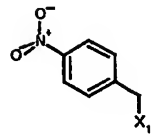
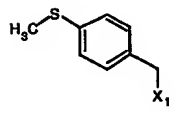
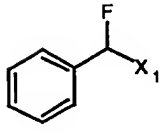
In a manner analogous to that of Examples 64 and 65, Examples 66-200 listed in the table below were prepared from Part A compound from Example 46 (0.1 mmol) and the respective carboxylic acid (0.3 mmol). A few compounds were purified by preparative HPLC, eluting with a gradient system of methanol and water with 0.2% trifluoroacetic acid. These compounds were isolated as trifluoroacetic acid salts.

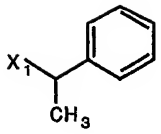
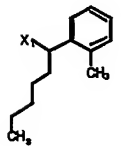
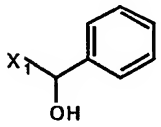
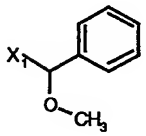
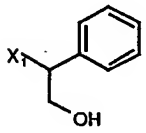
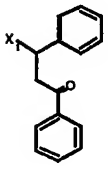
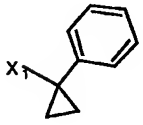
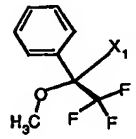
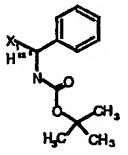
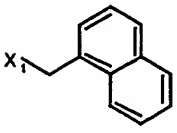


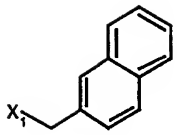
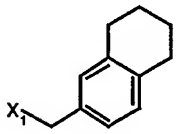
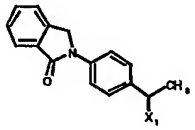
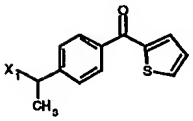
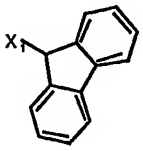
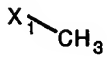
= X_1-R1

Example No.	X_1-R1	LC/MS (M + H)+
66		546
67		546
68		546
69		562

70		597
71		596
72		596
73		558
74		558
75		558
76		618
77		572
78		634
79		634

80		544
81		544
82		544
83		542
84		556
85		570
86		604
87		573
88		573
89		574
90		546

91		542
92		612
93		544
94		558
95		558
96		646
97		554
98		626
99		643
100		578

101		578
102		582
103		673
104		652
105		602
106		452
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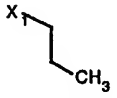
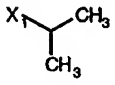
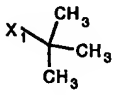
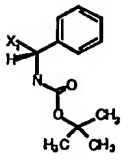
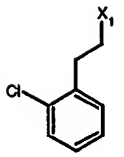
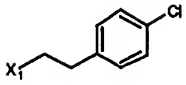
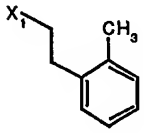
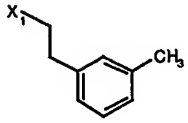
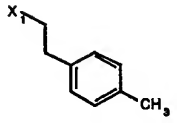
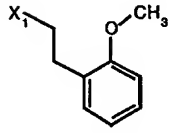
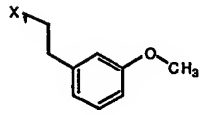
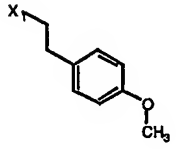
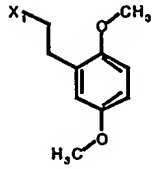
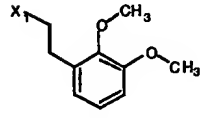
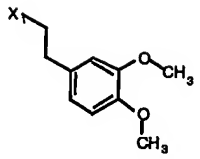
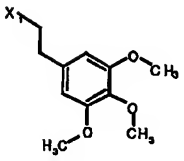
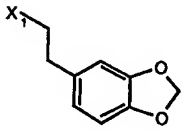
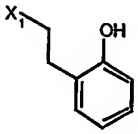
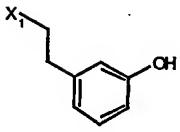
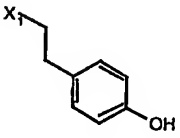
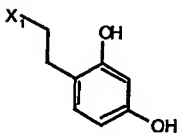
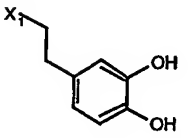
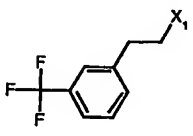
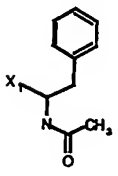
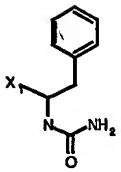
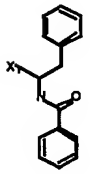
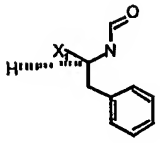
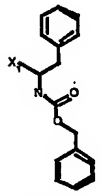
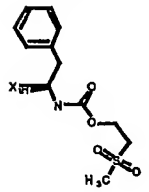
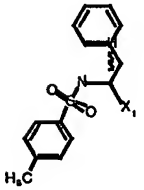
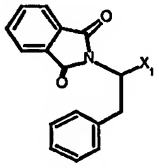
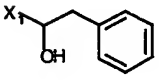
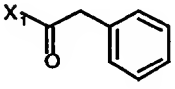
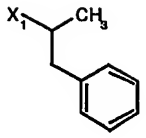
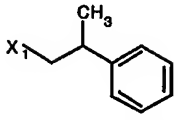
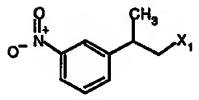
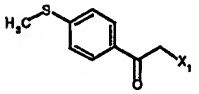
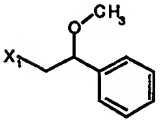
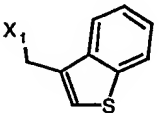
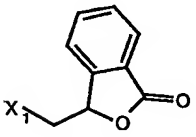
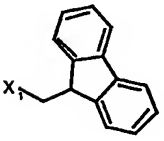
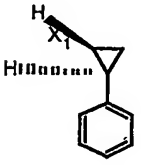
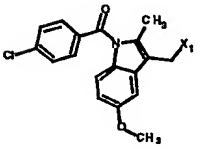
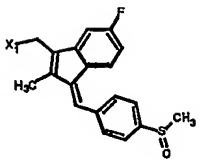
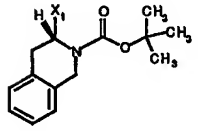
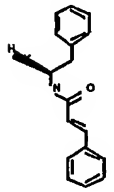
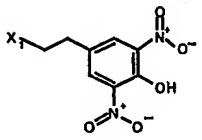
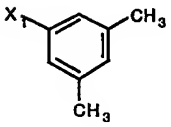
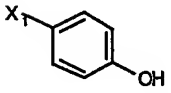
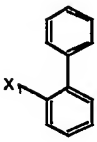
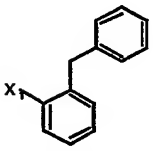
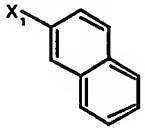
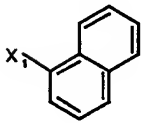
108		480
109		480
110		494
111		643

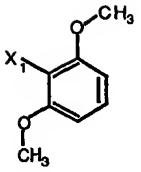
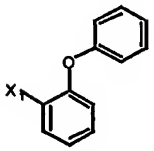
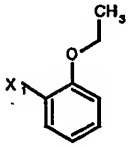
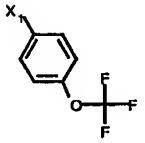
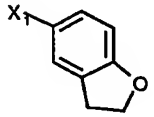
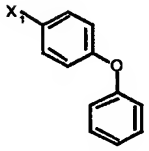
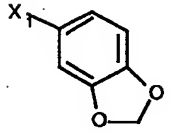
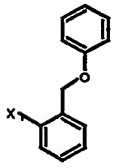
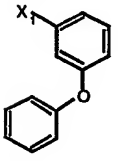
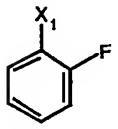
112		576
113		576
114		556
115		556
116		556
117		572
118		572
119		572
120		602
121		602

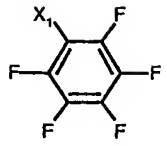
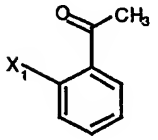
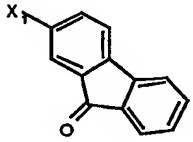
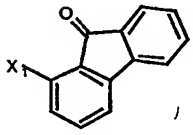
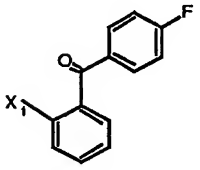
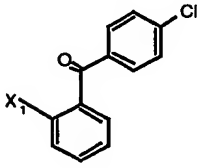
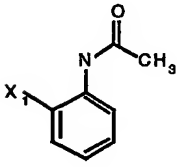
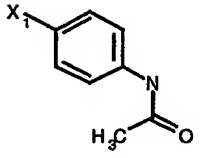
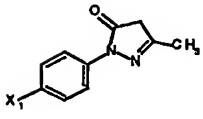
122		602
123		632
124		586
125		558
126		558
127		558
128		574
129		574
130		610
131		599

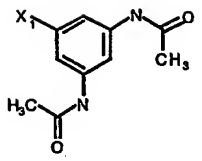
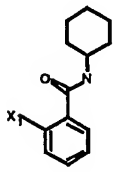
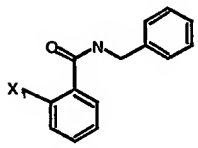
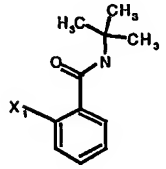
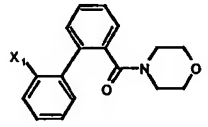
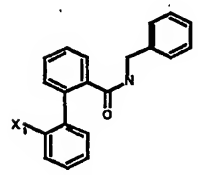
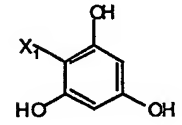
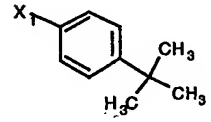
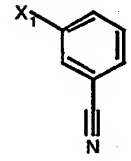
132		600
133		661
134		585
135		691
136		707
137		711
138		687
139		558
140		556

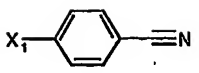
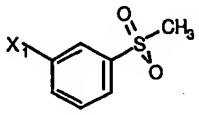
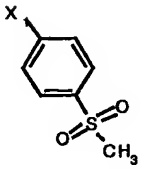
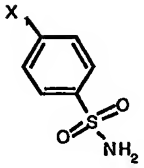
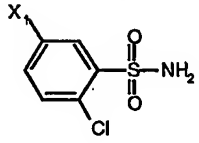
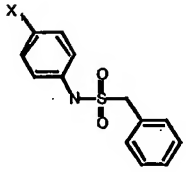
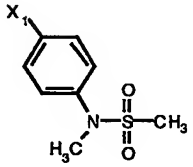
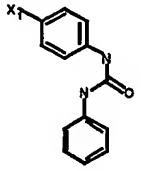
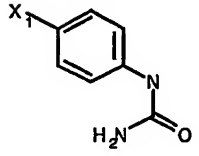
141		556
142		556
143		601
144		602
145		572
146		584
147		584
148		616
149		554
150		749

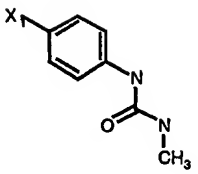
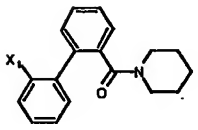
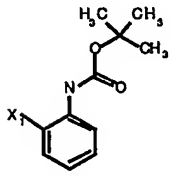
151		748
152		669
153		687
154		648
155		542
156		530
157		590
158		604
159		564
160		564

161		574
162		606
163		558
164		598
165		556
166		606
167		558
168		620
169		606
170		532

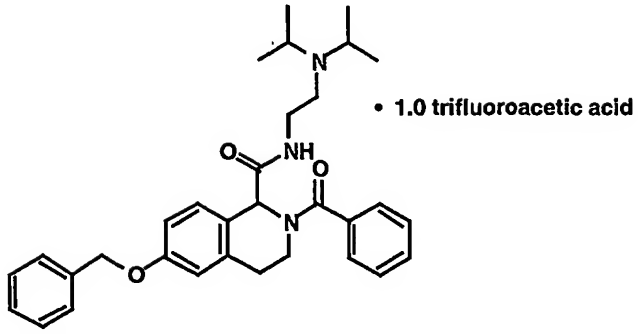
171		604
172		556
173		616
174		616
175		636
176		652
177		571
178		571
179		610

180		628
181		639
182		647
183		613
184		703
185		723
186		562
187		570
188		539

189		539
190		592
191		592
192		593
193		627
194		683
195		621
196		648
197		572

198		586
199		701
200		629

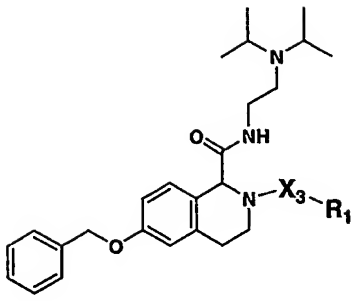
Example 201



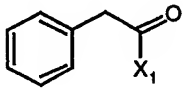
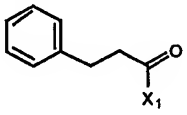
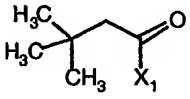
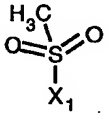
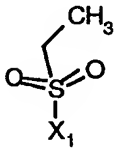
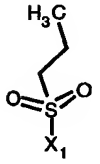
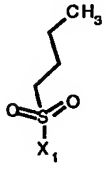
To a 0°C solution of benzoyl chloride (28.1 mg, 0.2 mmol) in dichloromethane (0.5 mL) was added Part A compound from Example 46 (61 mg, 0.15 mmol) followed by triethylamine (27 µL, 0.19 mmol). The reaction mixture was stirred at ambient temperature under nitrogen overnight and then was concentrated. The residue was partitioned between ethyl acetate and water. The two layers were separated, and the ethyl acetate layer was concentrated. Purification by preparative HPLC, eluting with 30-100% B (where A = 90% water, 10% methanol, 0.2% trifluoroacetic acid and B = 90% methanol, 10% water, 0.2% trifluoroacetic acid), gave the title compound (61.5 mg, 66%) as a pale yellow semi-solid/oil: LC/MS (electrospray, + ions) m/z 514 (M+H).

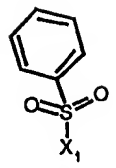
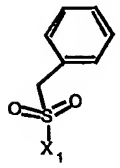
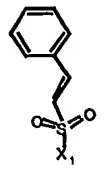
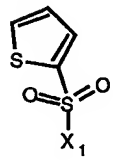
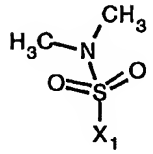
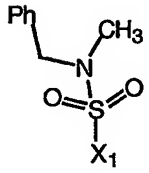
Examples 202 to 214

In a manner analogous to that of Example 201, Examples 202-214 in the table below were prepared from Part A compound from Example 46 and the respective acid chloride, sulfonyl chloride, sulfamoyl chloride.



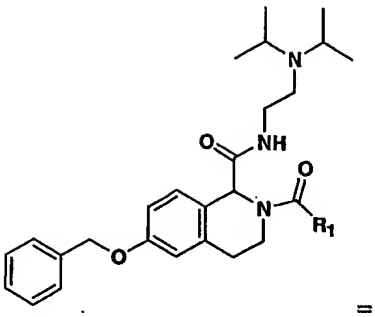
= X_1-X3-R1

Example No.	X_1-X3-R1	LC/MS (M + H)+
202		528
203		542
204		508
205		488
206		502
207		516
208		530

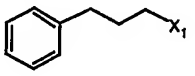
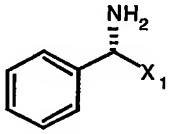
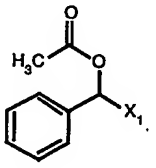
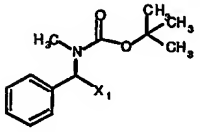
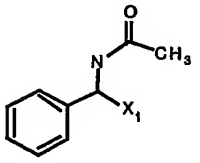
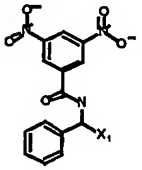
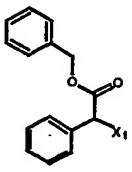
209		550
210		564
211		576
212		556
213		517
214		593

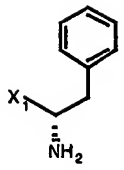
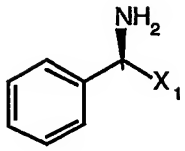
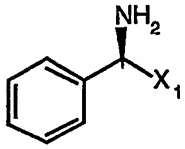
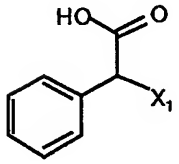
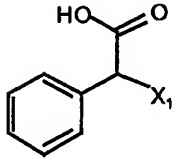
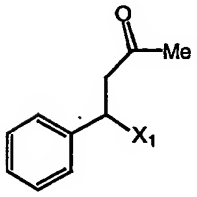
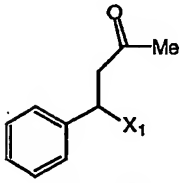
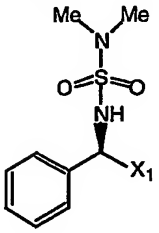
Examples 215 to 229

Examples 215-229 were prepared by methods described in earlier examples and by methods known in the art starting from Part A compound from Example 46 and the corresponding carboxylic acid.

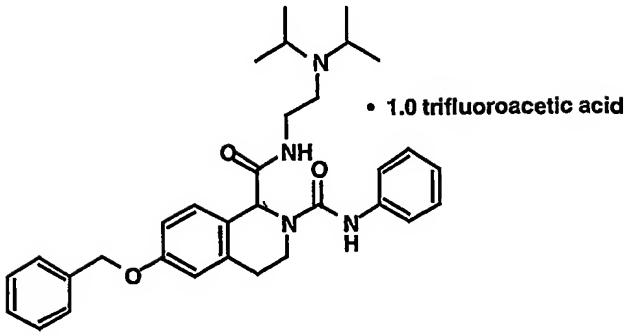


= X_1-R1

Example No.	X_1-R1	LC/MS $(M + H)^+$
215		556
216		543
217		586
218		657
219		585
220		737
221		662

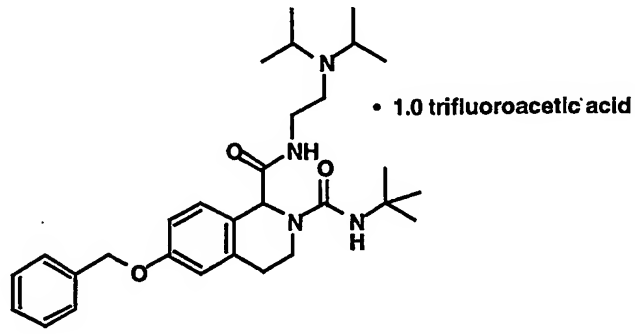
222		557
223		543
224		543
225		572
226		572
227 Isomer A		584
228 Isomer B		584
229		650

Example 230



To a solution of Part A compound from Example 46 (61 mg, 0.15 mmol) in dichloromethane (0.5 mL) was added phenyl isocyanate (19.7 mg, 0.165 mmol) via a syringe. Additional dichloromethane (0.5 mL) was added. The reaction mixture was stirred overnight, and then it was concentrated. Purification on preparative HPLC, eluting with a gradient system of 30-100% B (where A = 90% water, 10% methanol, 0.2% trifluoroacetic acid and B = 90% methanol, 10% water, 0.2% trifluoroacetic acid), gave the title compound (81 mg, 85%) as a white foam: HPLCb rt = 3.70 min.; LC/MS (electrospray, + ions) m/z 529 (M+H).

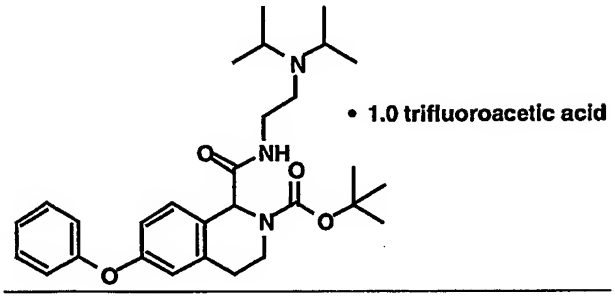
Example 231



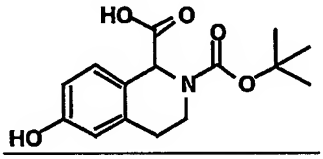
In a manner analogous to that of Example 230, the title compound was prepared from Part A compound from Example 46 (61 mg, 0.15 mmol) and *tert*-butyl isocyanate (16.4 mg, 0.165 mmol) in a yield of 69.5 mg (75%) as a

white semi-solid/oil: HPLCb rt = 3.71 min.; LC/MS (electrospray, + ions) m/z 509 (M+H).

Example 232

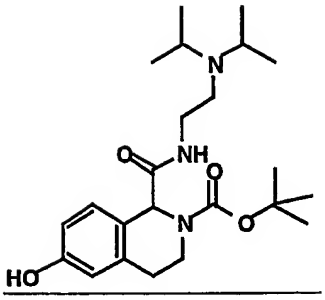


A.



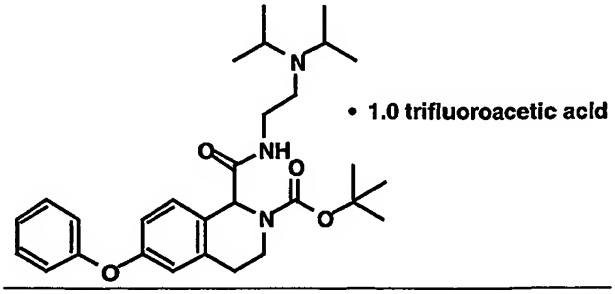
To a solution of Part C compound from Example 1 (1.00 g, 3.25 mmol) in methanol (1 mL) and tetrahydrofuran (1 mL) was added a solution of sodium hydroxide (260 mg, 6.5 mmol) in water (650 µL). The reaction was stirred overnight at ambient temperature, heated at 60°C for 6 h and then stirred at ambient temperature overnight. The solvent was removed *in vacuo*, and the residue was partitioned between water and ethyl acetate. The aqueous layer was separated and acidified with 6 N hydrochloric acid solution to pH ~3 and extracted with ethyl acetate (2x) The organic layers were dried over sodium sulfate and the mixture was filtered. The filtrate was concentrated to give the title compound (930 mg, 97.5%) as a clear oil, which became a white foam.

B.



To a solution of Part A compound (500 mg, 1.7 mmol) and diisopropylethylenediamine (326 µL, 1.9 mmol) in dimethylformamide (10 mL) was added diisopropylethylamine (890 µL, 5.1 mmol) followed by 1-hydroxy-7-azabenzotriazole (325 mg, 2.4 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (327 mg, 1.7 mmol). After stirring the reaction mixture overnight, the mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was washed with water (2x) and brine, and then dried over sodium sulfate. The mixture was filtered and the filtrate concentrated *in vacuo* to give the title product (587 mg, 82.1%) as a white foam.

C.



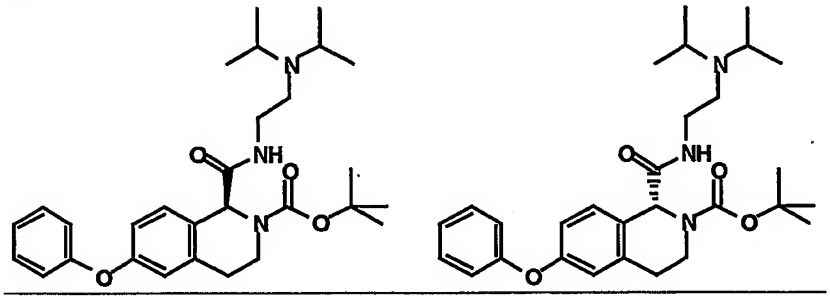
To a slurry of Part B compound (50 mg, 0.12 mmol), phenyl boronic acid (29 mg, 0.24 mmol), copper(II) acetate (22 mg, 0.12 mmol) and 4 Å powdered molecular sieves in dichloromethane (1.2 mL) was added pyridine (48 µL, 0.60 mmol). The reaction was stirred overnight and then was filtered. The filtrate was concentrated to a

green oil that was purified by preparative HPLC. The title compound (59 mg, 81%) was obtained as a yellow oil: : HPLCa1 rt = 2.2 min.; LC/MS (electrospray, + ions) m/z 496 (M+H).

Example 233

Isomer A and Isomer B

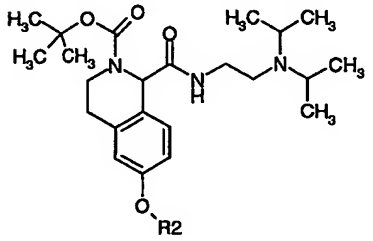
A.



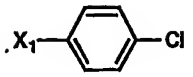
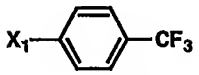
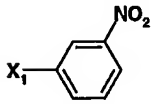
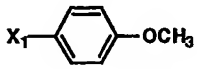
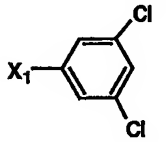
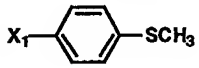
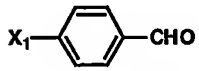
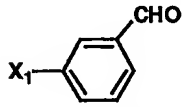
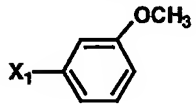
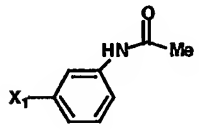
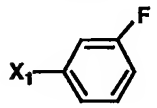
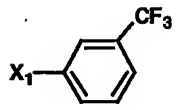
Title compound, Example 232 (70 mg) was resolved on Chiralpak AD column (50 x 500 mm), eluting with 20% isopropanol/hexanes to give the title compounds, Isomer A (28 mg) and Isomer B (30 mg).

Examples 234 to 245

In a manner analogous to that of Example 232, Examples 234-245 compounds listed in the table below were prepared from Part B compound from Example 232 (0.12 mmol) and the respective phenylboronic acid (0.24 mmol). A few compounds were purified by preparative HPLC, eluting with a gradient system of methanol and water with 0.2% trifluoroacetic acid. These compounds were isolated as trifluoroacetic acid salts.

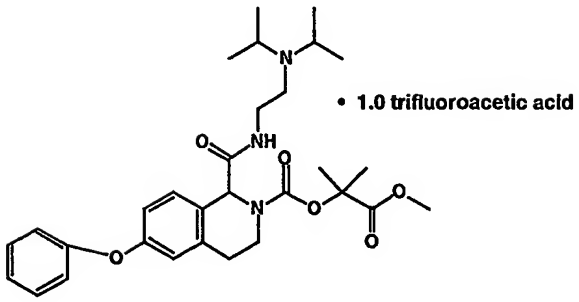


= X_1-R2

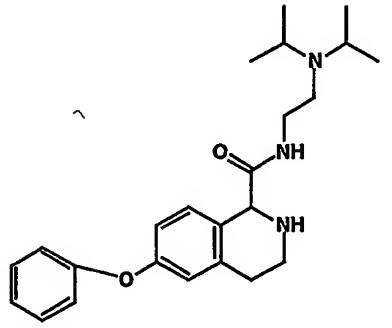
Example No.	X_1-R2	LC/MS (M + H)+
234		531
235		564
236		541
237		526
238		565
239		542
240		524
241		524
242		526
243		553
244		514
245		564

5

Example 246

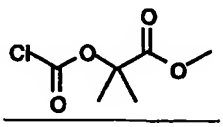


A.



To neat title compound from Example 232 (1.56 g, 3.15 mmol) is added 4N hydrogen chloride (7 mL, dioxane solution) at room temperature. After 3 h, the volatiles were removed in vacuo, the residue redissolved in ethyl acetate and the pH adjusted to 8 with 1N sodium hydroxide. The organic layer was dried and concentrated to give the title compound (1.11 g) as a yellow colored oil. LC/MS (electrospray, + ions) m/z 396(M+H).

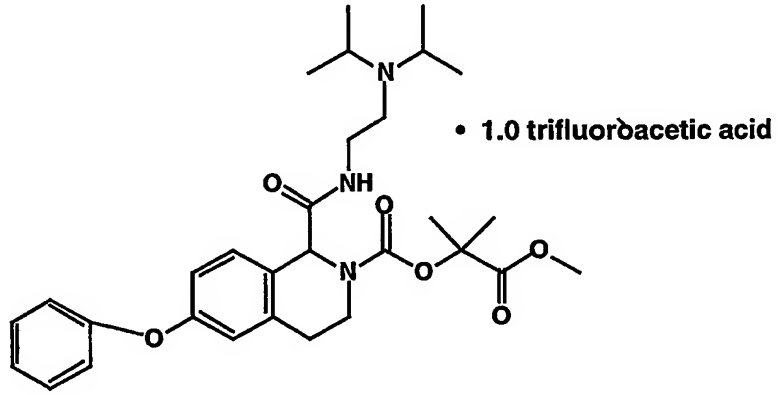
B.



To a 0°C solution of methyl 2-hydroxyisobutyrate (236 mg, 2.0 mmol) and triethylamine (202 mg, 2.0 mmol)

in tetrahydrofuran (5 mL) was added 1.9 M phosgene in toluene (1.68 mL, 3.2 mmol). After stirring for 2 h between -5 to 0°C, the reaction mixture was concentrated and used in the next procedure without purification.

C.

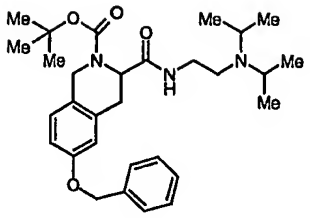
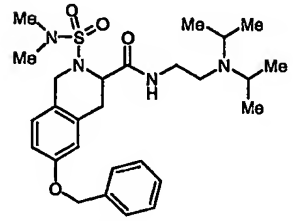
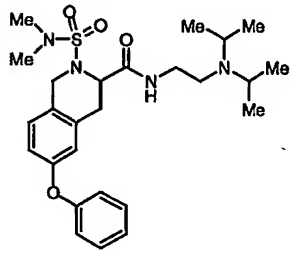


At 0°C, a solution of Part B compound (2.0 mmol) in dichloromethane (5 mL) was treated with Part A compound(118.9 mg, 0.30 mmol) followed by triethylamine (101.2 mg, 1.0 mmol). The reaction mixture was stirred at 0°C to 5°C for 2 h and then concentrated. Purification by preparative HPLC, eluting with a gradient system of 40-100% B (where A = 90% water, 10% methanol, 0.2% trifluoroacetic acid and B = 90% methanol, 10% water, 0.2% trifluoroacetic acid), gave the title compound (115.8 mg) as a yellow oil; LC/MS (electrospray, + ions) m/z 540(M+H).

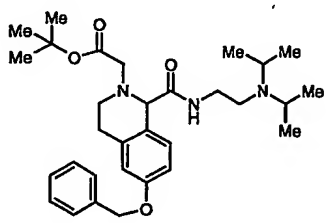
Examples 247 to 250

Examples 247-250 listed below can were prepared as shown in Scheme 11 and employing the procedures described above, the working examples, and methods known in the arts.

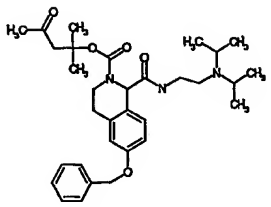
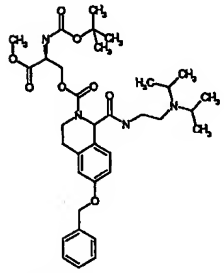
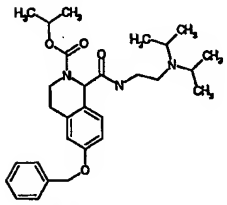
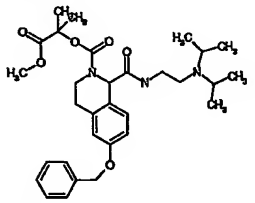
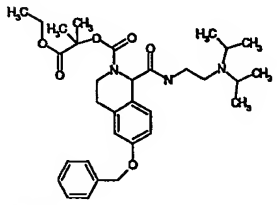
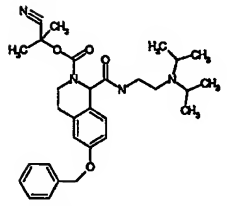
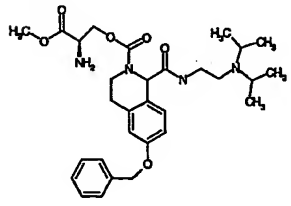
Example No.	Structure	LC/MS (M + H)+

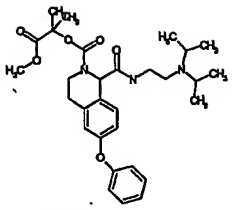
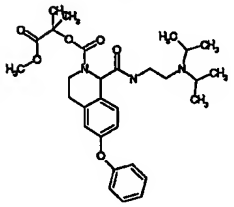
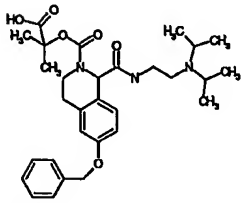
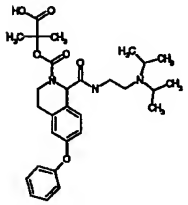
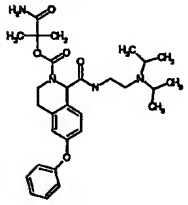
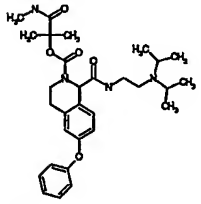
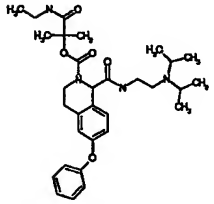
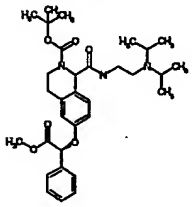
247		510
248		517
249		503

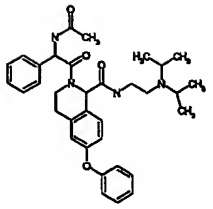
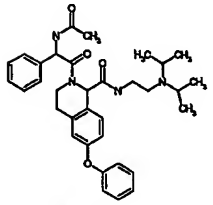
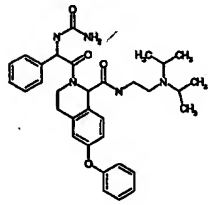
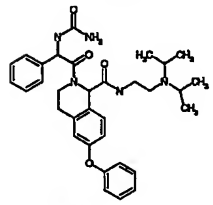
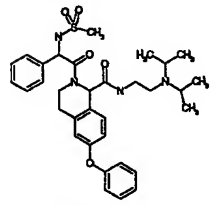
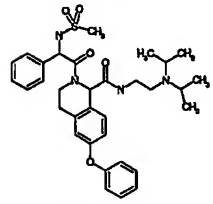
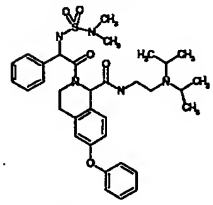
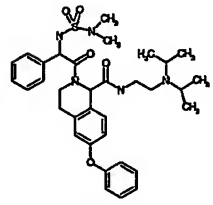
Examples listed below can be prepared from intermediate Part A compound from Example 46 and an alkyl halide:

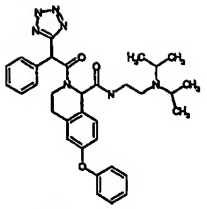
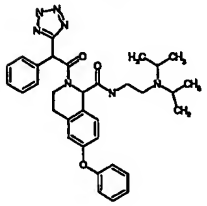
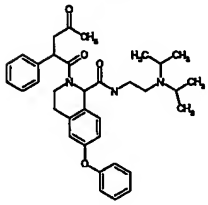
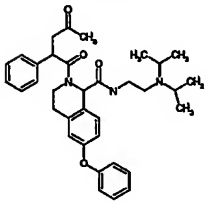
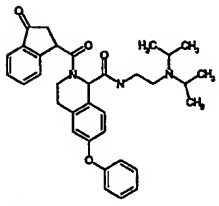
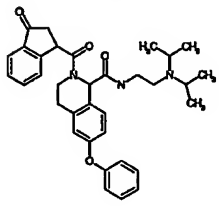
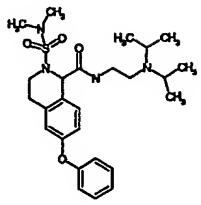
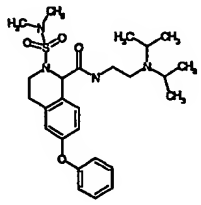
Example No.	Structure	LC/MS (M + H)+
250		524

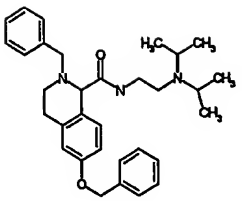
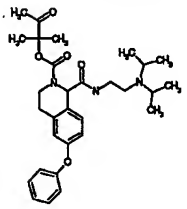
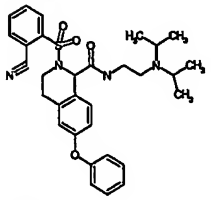
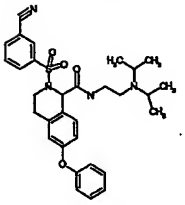
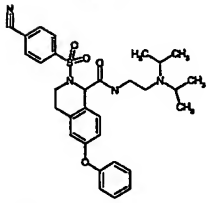
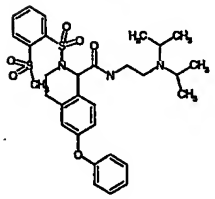
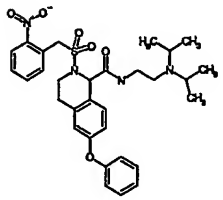
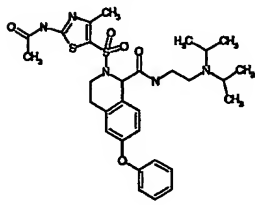
Examples listed in the Table below can be prepared employing the procedures described above, the working examples, and methods known in the arts.

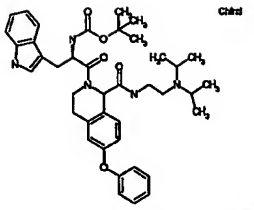
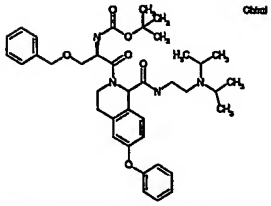
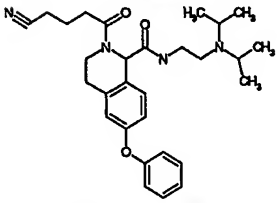
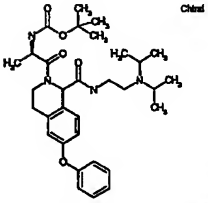
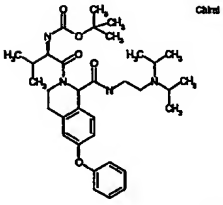
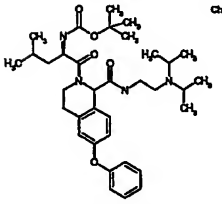
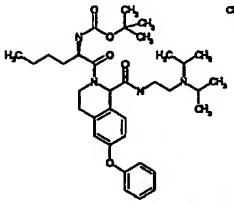
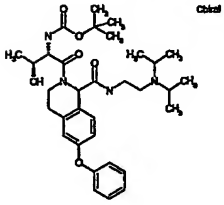
Example No.	Structure	LC/MS (M+H)+
251		552
252		655
253		496
254		554
255		568
256		521
257		555

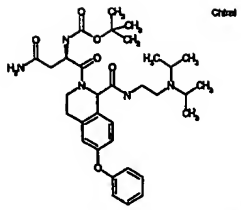
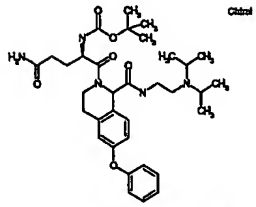
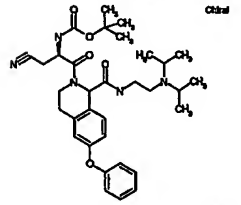
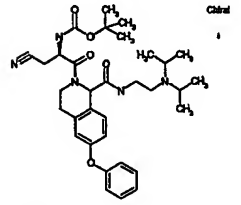
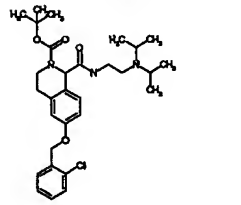
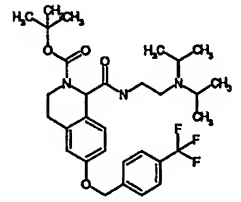
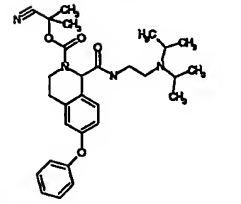
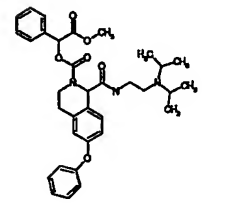
258 Isomer A		540
259 Isomer B		540
260		540
261		526
262		525
263		539
264		553
265		568

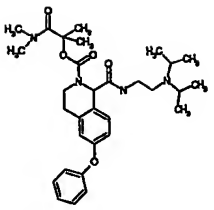
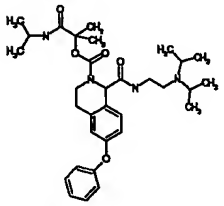
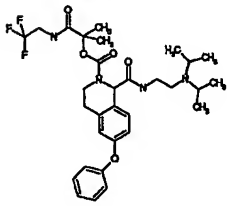
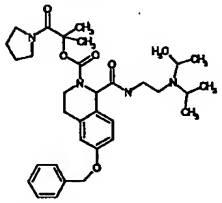
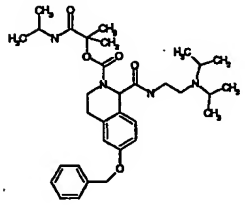
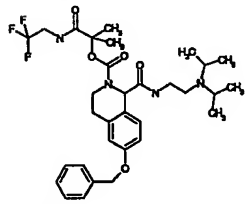
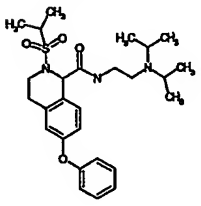
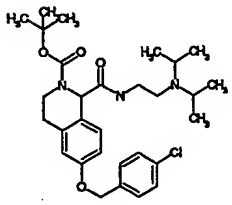
266 Diastereomer A		571
267 Diastereomer B		571
268 Diastereomer A		572
269 Diastereomer B		572
270 Diastereomer A		607
271 Diastereomer B		607
272 Diastereomer A		636
273 Diastereomer B		636

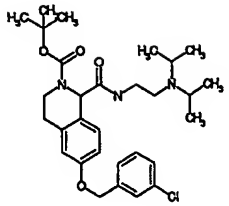
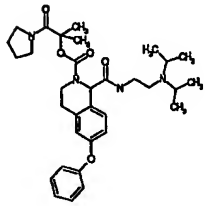
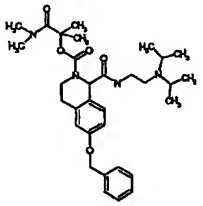
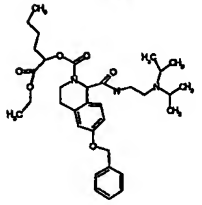
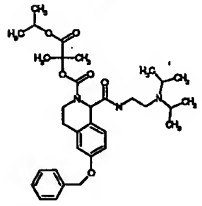
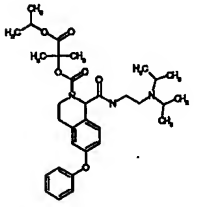
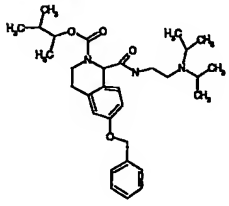
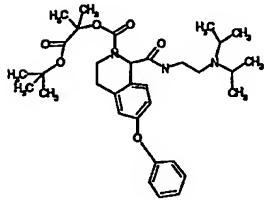
274 Diastereomer A		582
275 Diastereomer B		582
276 Diastereomer A		570
277 Diastereomer B		570
278 Diastereomer A		554
279 Diastereomer B		554
280 Isomer A		503
281 Isomer B		503

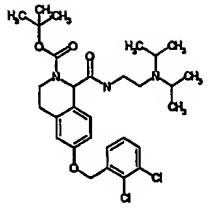
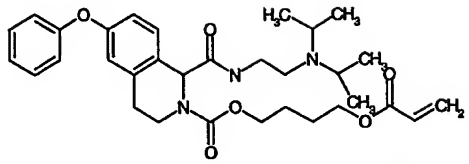
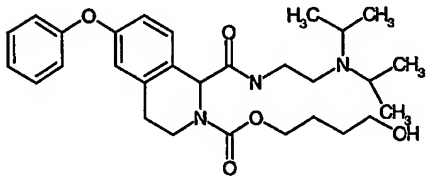
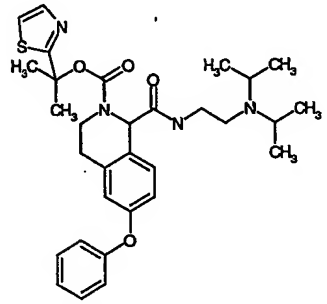
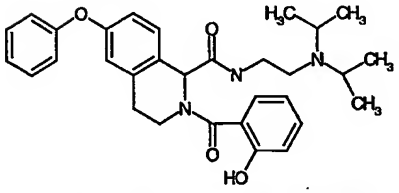
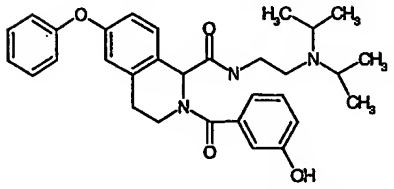
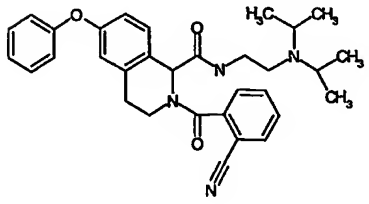
282		500
283		524
284		561
285		561
286		561
287		614
288		595
289		614

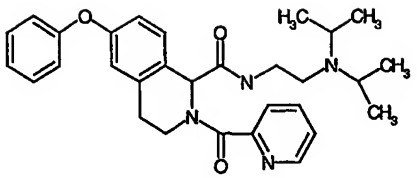
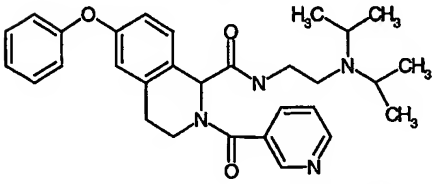
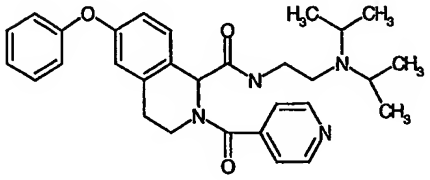
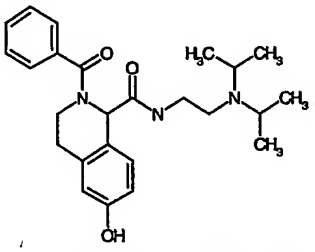
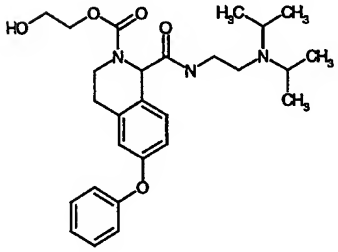
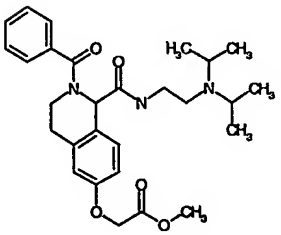
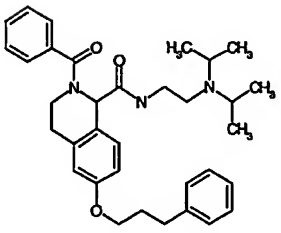
290		682
291		673
292		491
293		567
294		595
295		609
296		609
297		597

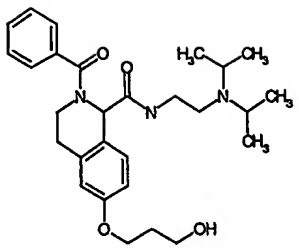
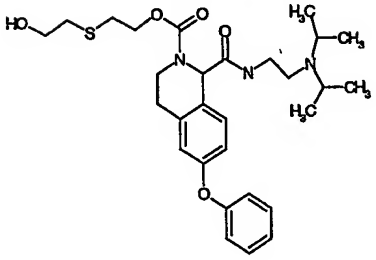
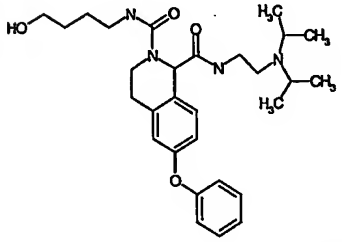
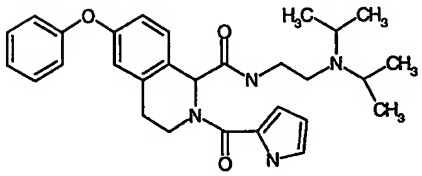
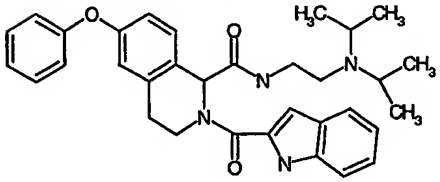
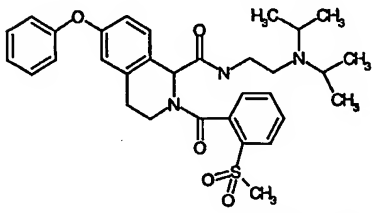
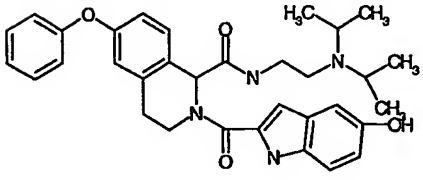
298		610
299		624
300		592
301		592
302		545
303		578
304		507
305		588

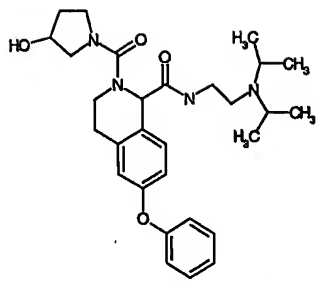
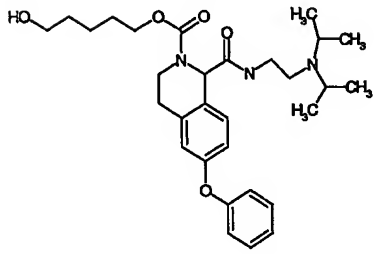
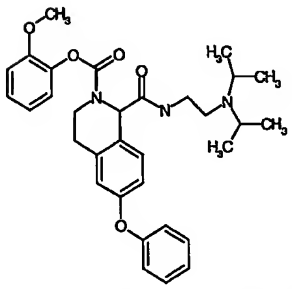
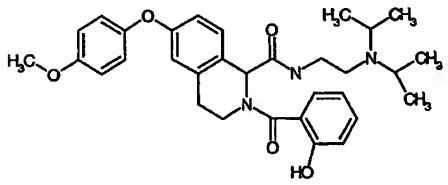
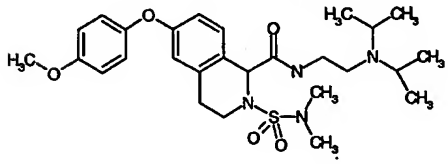
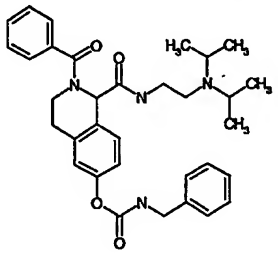
306		553
307		567
308		607
309		593
310		581
311		621
312		502
313		545

314		545
315		579
316		567
317		596
318		582
319		568
320		524
321		582

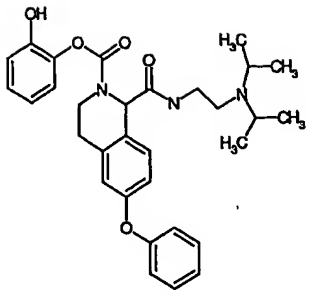
322		579
323		566
324		512
325		565
326		516
327		516
328		525

329		501
330		501
331		501
332		424
333		484
334		496
335		542

336		482
337		544
338		511
339		489
340		539
341		587
342		555

343		509
344		526
345		546
346		546
347		533
348		557

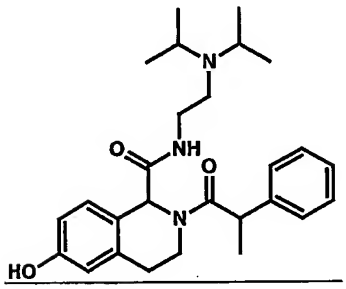
349



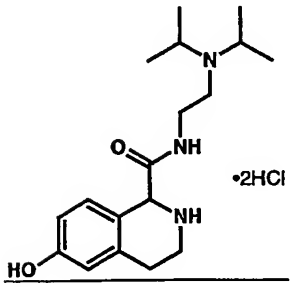
532

Example 350

Isomer A and Isomer B



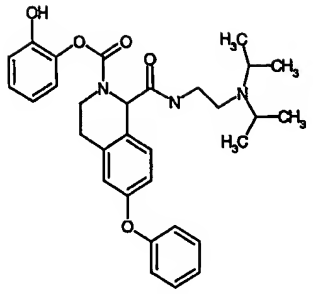
A.



Part B compound from Example 232 (0.1 g, 0.25 mmol) was dissolved in 4 *M* HCl in dioxane (2 mL) and stirred at room temperature for 1 hour. Concentration in vacuo gave the crude hydrochloride salt that was used in the next step.

B.

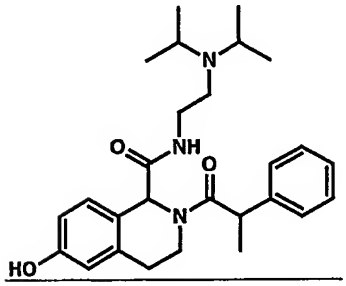
349



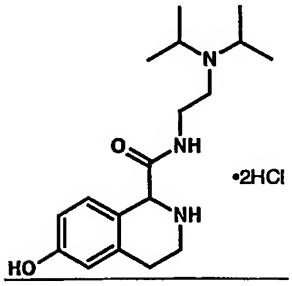
532

Example 350

Isomer A and Isomer B

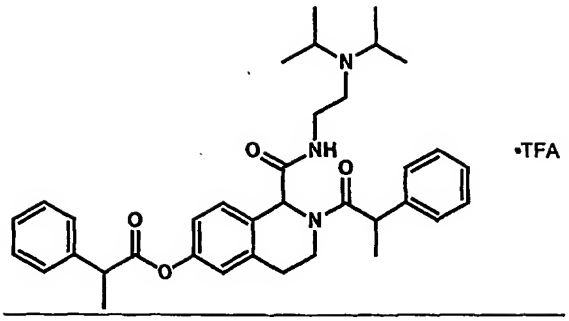


A.



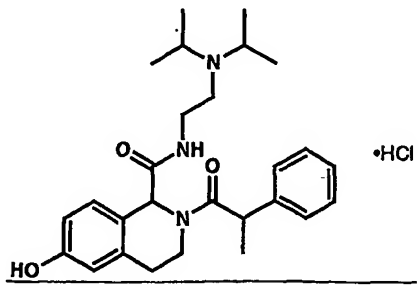
B.

Part B compound from Example 232 (0.1 g, 0.25 mmol) was dissolved in 4 *M* HCl in dioxane (2 mL) and stirred at room temperature for 1 hour. Concentration in vacuo gave the crude hydrochloride salt that was used in the next step.



A solution of Part A compound (0.1 g, 0.25 mmol), 2-phenylethanoic acid (0.14 g, 0.94 mmol), diisopropylethylamine (0.08 g, 0.63 mmol) and hydroxybenzotriazole (0.105 g, 0.78 mmol) in DMF (3 mL) was stirred for 10 minutes. To this solution was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.149 g, 0.78 mmol) and the mixture was stirred at room temperature for 20 hours. The reaction was diluted with ethyl acetate and washed with water, saturated $NaHCO_3$, and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give the crude product. A small amount of this was purified using preparative HPLC to give the trifluoroacetate salt as a colorless oil: HPLCb rt=3.28 and 3.36 min; LC/MS (electrospray, + ions) m/z 584.3 (M+H).

C.

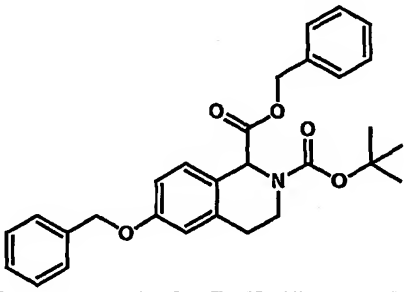


To a solution of Part B compound (0.1 g, 0.14 mmol) in methanol (1 mL) was added 2 *N* NaOH (1 mL) and the mixture stirred at room temperature for 1 hour. The reaction was concentrated in vacuo and the residue was dissolved in ethyl acetate and acidified with 1 *N* HCl to

~pH 1. This mixture was extracted with ethyl acetate (3x100 mL). The organic layers were combined, washed with saturated $NaHCO_3$, brine and dried over sodium sulfate, filtered and concentrated in vacuo to give the product as a white solid (32 mg): HPLCb rt=2.41 min; LC/MS (electrospray, + ions) m/z 452.3 (M+H).

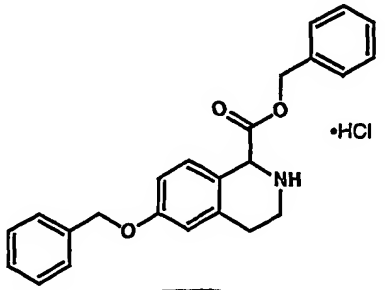
Examples 351-388

A.



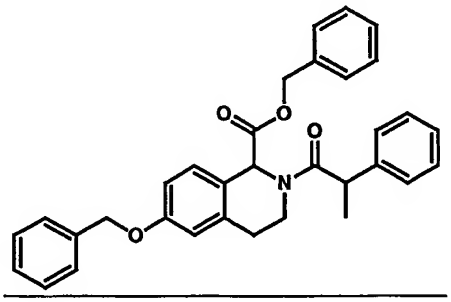
To a solution of Part A compound from Example 232 (1.0 g, 3.4 mmol) and potassium carbonate (2.0 g, 14.4 mmol) in DMF (10 mL) was added benzyl bromide (0.98 mL, 8.2 mmol) and the reaction stirred at room temperature for 4 hours. The mixture was concentrated in vacuo, the residue dissolved in ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the crude product (1.4 g).

B.



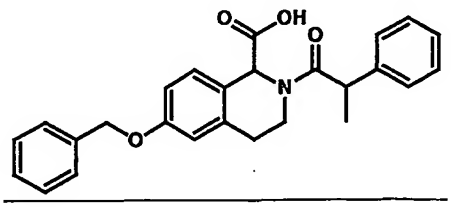
Part A compound (1.4 g, 2.9 mmol) was dissolved in 4 *N* HCl in dioxane (4 mL) and stirred for 2 hours. The mixture was concentrated in vacuo to give the crude hydrochloride salt (1.2 g).

C.



To a solution of Part B compound (1.2 g, 2.9 mmol), 2-phenylpropionic acid (0.59 mL, 4.4 mmol), diisopropylethylenediamine (0.5 mL, 3.0 mmol), and hydroxybenzotriazole (500 mg, 3.8 mmol) in dichloromethane (15 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (750 mg, 3.9 mmol) and the mixture was stirred at room temperature for 20 hours. The reaction was diluted with ethyl acetate and washed with water, saturated $NaHCO_3$, and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give the crude product.

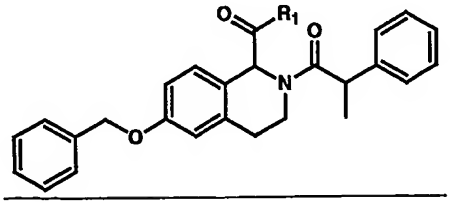
D.



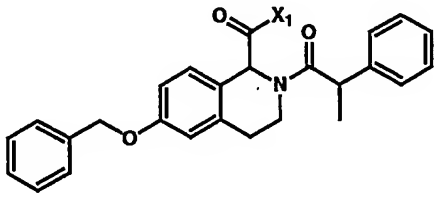
To a solution of Part C compound (1.5 g, 2.9 mmol) in methanol (1 mL), THF (1 mL), was added 10 *M* sodium hydroxide (0.7 mL, 7 mmol) and the mixture was stirred for 16 hours. The reaction mixture was transferred to a

separatory funnel, acidified with 1 *N* HCl and extracted with ethyl acetate. The organic layers were combined, washed with brine, and dried over magnesium sulfate. The mixture was filtered and concentrated to give the product as a white solid.

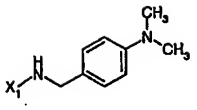
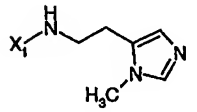
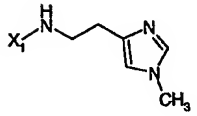
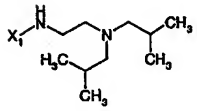
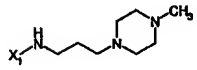
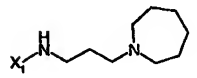
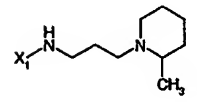
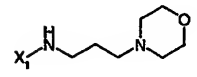
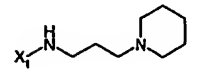
E.

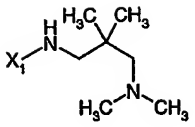
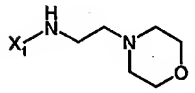
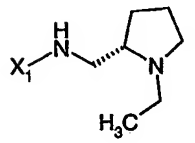
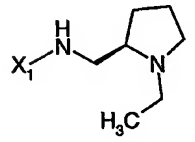
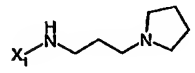
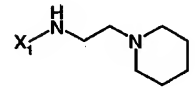
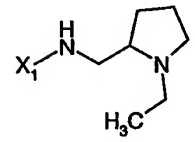
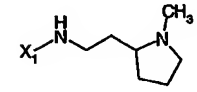
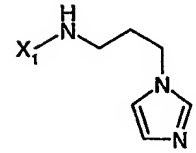


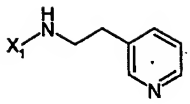
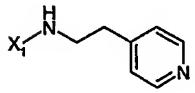
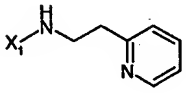
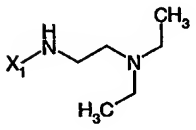
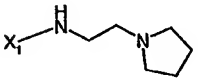
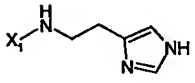
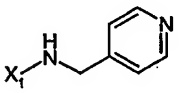
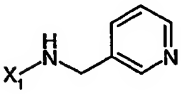
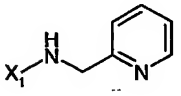
The compounds shown in the table below were synthesized in library format starting with Part D compound. Part D compound (200 µL of a 0.225 *M* solution in dichloromethane, 0.045 mmol), the appropriate amine (150 µL of a 0.20 *M* solution in dichloromethane, 0.030 mmol), and 1-hydroxybenzotriazole (0.045 mmol) and diisopropylcarbodiimide (0.045 mmol) in 250 µL DMF were stirred at room temperature for 16 hours. The reaction mixtures were loaded onto ion exchange cartridges (SCX, 0.5 g), washed with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), 2 *M* NH_3 in methanol. The concentrated ammonia fractions were collected and concentrated to give the desired products which gave the analytical data shown.

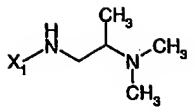
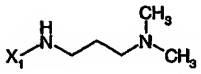
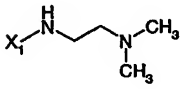
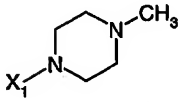
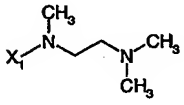
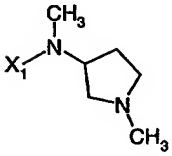
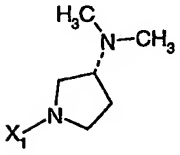
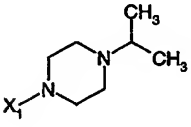
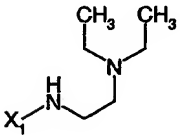


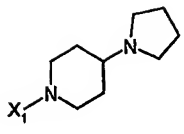
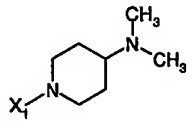
Example No.	X_1-R_1	Calc MW	= X_1-R_1 LC/MS $(M + H)^+$

351		547.7	548.5
352		522.7	523.48
353		522.7	523.48
354		569.8	570.55
355		554.7	555.55
356		553.8	554.53
357		553.8	554.77
358		541.7	542.51
359		539.7	540.51

360		527.7	528.52
361		527.7	528.49
362		525.7	526.51
363		525.7	526.49
364		525.7	526.51
365		525.7	526.5
366		525.7	526.5
367		525.7	526.52
368		522.7	523.46

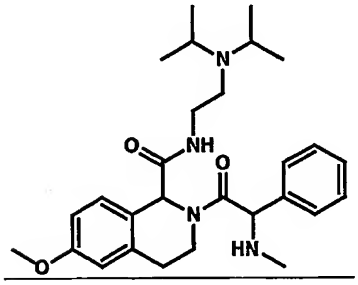
369		519.7	520.45
370		519.7	520.48
371		519.7	520.44
372		513.7	514.53
373		511.7	512.53
374		508.6	509.45
375		505.6	506.44
376		505.6	506.48
377		505.6	506.45

378		499.7	500.51
379		499.7	500.48
380		485.6	486.47
381		497.6	498.49
382		499.7	500.52
383		511.7	512.5
384		511.7	512.49
385		525.7	526.54
386		527.7	528.52

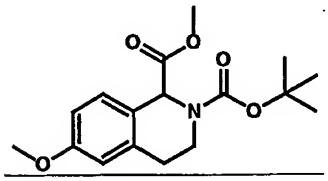
387		551.7	552.52
388		525.7	526.52

Example 389

Isomer A and Isomer B

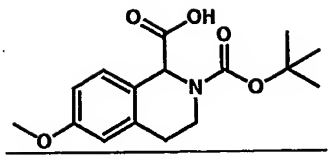


A.



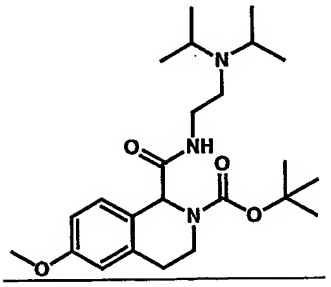
To a solution of Part A compound from Example 232 (2 g, 6.8 mmol) and potassium carbonate (3.8 g, 27 mmol) in DMF (5 mL) was added methyl iodide (0.877 mL, 14 mmol) and the reaction stirred at room temperature for 4 hours. The mixture was concentrated in vacuo, the residue dissolved in ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the crude product (2 g).

B.



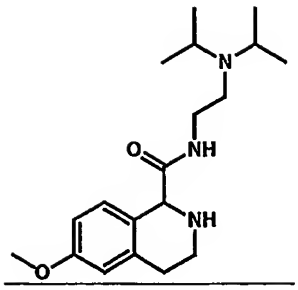
To a solution of Part A compound (2.0 g, 6.2 mmol) in methanol (10 mL), THF (10 mL), and water (10 mL) was added NaOH (820 mg, 20 mmol) and the mixture was stirred for 25 hours. The reaction mixture was transferred to a separatory funnel, acidified with 1 *N* HCl and extracted with ethyl acetate. The organic layers were combined, dried over magnesium sulfate, filtered and concentrated to give the product as a white solid (1.8 g).

C.



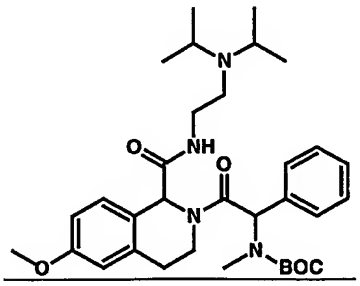
A solution of Part B compound (0.1 g, 0.3 mmol), diisopropylethylenediamine (52 mg, 0.36 mmol), and hydroxybenzotriazole (62 mg, 0.46 mmol) in DMF (2 mL) was stirred for 10 minutes. To this solution was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (72 mg, 0.36 mmol) and the mixture was stirred at room temperature for 20 hours. The reaction was diluted with ethyl acetate and washed with water, saturated $NaHCO_3$, and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give the crude product (0.15 g).

D.



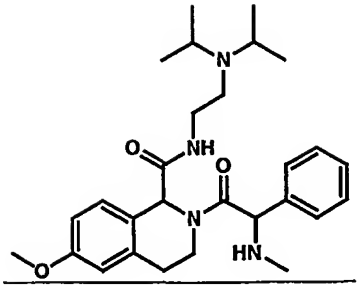
Part C compound (0.15 g, 0.35 mmol) was dissolved in 4 *M* HCl in dioxane (1 mL) and stirred at room temperature for 1 hour. Concentration in vacuo gave the crude hydrochloride salt. This was purified using an ion exchange column (SCX) eluting with 2 *N* NH_3 in methanol, followed by chromatography (silica gel, 15% MeOH in CH_2Cl_2 with 0.5% triethylamine, and a second pass through ion exchange resin to give the pure amine as the free base.

E.



A solution of Part D compound (11 mg, 0.033 mmol), *N*-BOC-*N*-methylphenylglycine (12 mg, 0.045 mmol), diisopropylcarbodiimide (7 mL, 0.45 mmol) and 1-hydroxy-7-azabenzotriazole (6.1 mg, 0.45 mmol) in DMF (0.5 mL) and dichloromethane (0.5 mL) was stirred at room temperature for 16 hours. The reaction mixture was loaded onto an ion exchange cartridge (SCX, 0.5 g), washed with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), 2 *M* NH_3 in methanol. The concentrated ammonia fractions were collected and concentrated to give the desired product (6.5 mg).

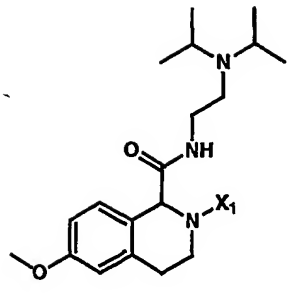
F.



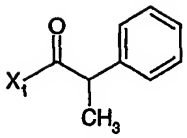
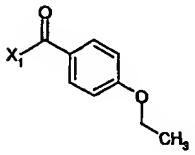
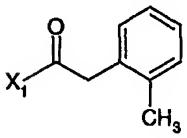
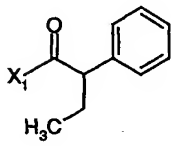
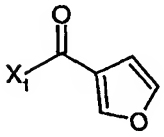
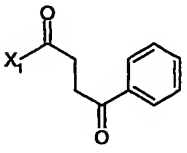
A solution of Part E compound (6.5 mg, 0.014 mmol) in 4 *M* HCl in dioxane (0.3 mL) was stirred at room temperature for 4 hours. The reaction mixture was loaded onto an ion exchange cartridge (SCX, 0.5 g), washed with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), 2 *M* NH_3 in methanol. The concentrated ammonia fractions were collected and concentrated to give the desired product (5 mg): HPLCb rt=1.8 and 2.0 min; LC/MS (electrospray, + ions) m/z 481.5 (M+H).

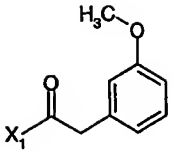
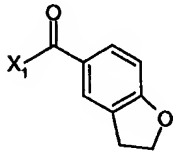
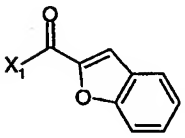
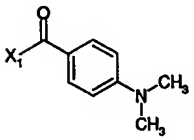
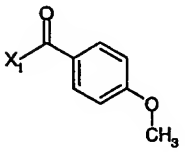
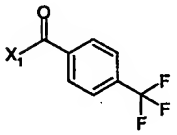
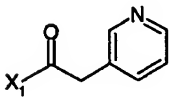
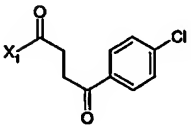
Examples 390-437

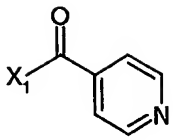
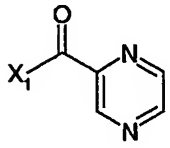
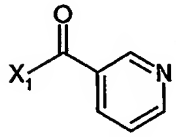
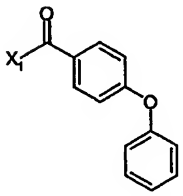
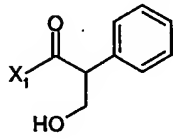
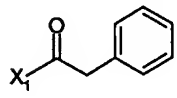
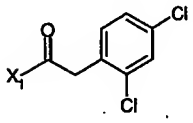
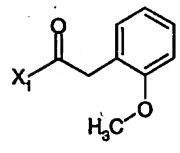
The compounds shown in the table below were synthesized in library format starting with Part D compound from Example 389. Part D compound from Example 61 (500 µL of a 0.06 *M* solution in dichloromethane, 0.03 mmol), the appropriate acid (300 µL of a 0.15 *M* solution in dichloromethane, 0.045 mmol), 1-hydroxy-7-azabenzotriazole (0.045 mmol), and diisopropylcarbodiimide (0.045 mmol) in 200 µL DMF were stirred at room temperature for 16 hours. The reaction mixtures were loaded onto ion exchange cartridges (SCX, 0.5 g), washed with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), 2 *M* NH_3 in methanol. The concentrated ammonia fractions were collected and concentrated to give the desired products which gave the analytical data shown.

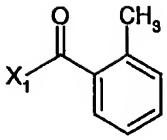
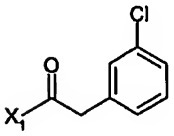
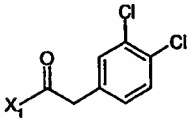
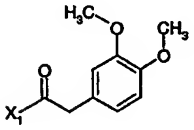
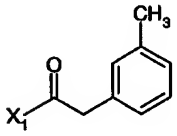
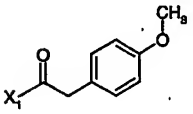
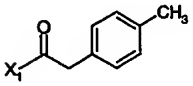
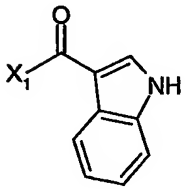


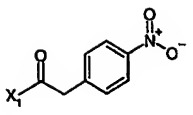
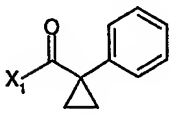
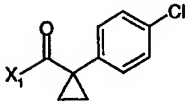
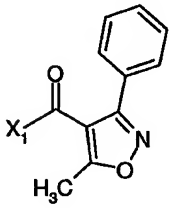
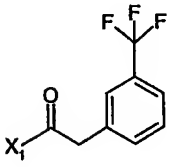
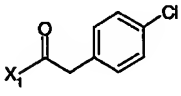
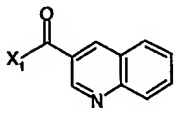
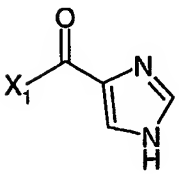
= X_1-R_1

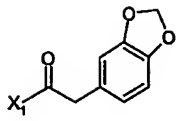
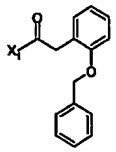
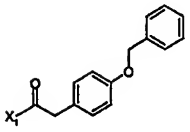
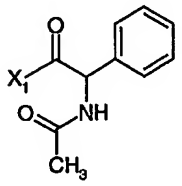
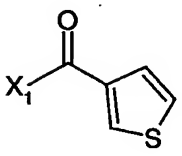
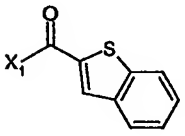
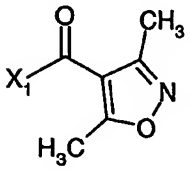
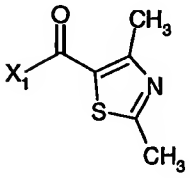
Example No.	X_1-R_1	Calc MW	LC/MS $(M + H)^+$
390		465.64	466.5
391		481.6	480.49 (M-H)-
392		465.6	466.61
393		479.7	480.62
394		427.6	428.68
395		493.7	494.75

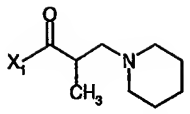
396		481.6	482.75
397		479.6	480.75
398		477.6	478.72
399		480.7	479.52 (M-H)-
400		467.6	468.45
401		505.6	506.56
402		452.6	453.59
403		527.3	528.46

404		438.6	439.74
405		439.6	440.46
406		438.6	439.51
408		529.7	530.59
409		481.6	482.74
410		451.6	452.73
411		519.2	520.43
412		481.6	482.61

413		451.6	452.59
414		485.2	486.55
415		519.2	520.41
416		511.7	512.75
417		465.6	466.61
418		481.6	482.58
419		465.6	466.62
420		476.6	477.5

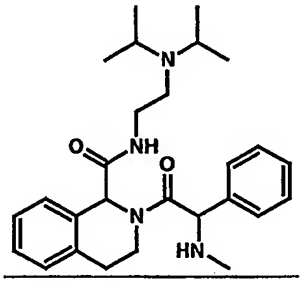
421		496.6	497.48
422		477.7	478.62
423		511.3	512.58
424		518.7	519.6
425		519.6	520.58
426		485.2	486.57
427		488.6	489.45
428		427.6	426.46 (M-H)-

429		495.6	496.6
430		557.7	558.63
431		557.7	558.64
432		508.7	509.63
433		443.6	444.54
434		493.7	494.55
435		456.6	457.59
436		472.7	473.45

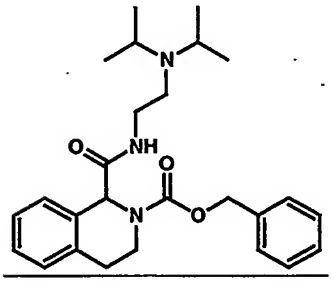
437		486.7	487.58

Example 438

Isomer A and Isomer B

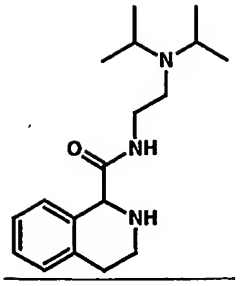


A.



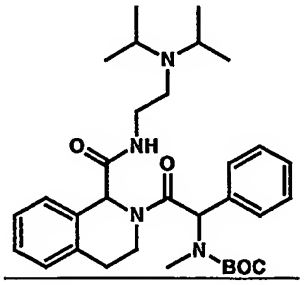
A solution of *N*-benzyloxycarbonyl-DL-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid (0.31 g, 1 mmol), prepared according to a published procedure in WO9312091, diisopropylethylenediamine (0.16 g, 1.1 mmol), and hydroxybenzotriazole (0.19 mg, 1.4 mmol) in DMF (3 mL) was stirred for 10 minutes. To this solution was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.21 g, 1.1 mmol) and the mixture was stirred at room temperature for 20 hours. The reaction was diluted with ethyl acetate and washed with water, saturated $NaHCO_3$, and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give the crude product (0.5 g).

B.



To a solution of Part A compound (2.2 g, 5.0 mmol) in ethanol (10 mL) and acetic acid (1 mL) was added 10% palladium on carbon (0.3 g). The flask was charged with hydrogen at atmospheric pressure and stirred for 16 hours. The reaction mixture was filtered through a pad of celite and concentrated to give the crude product (1.5 g). Purification using chromatography (silica gel, 15% methanol/dichloromethane with 0.5% triethylamine) gave the desired product as a white solid.

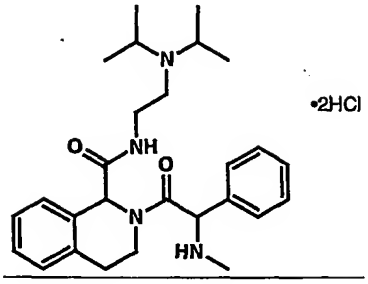
C.



A solution of Part B compound (10 mg, 0.033 mmol), *N*-BOC-*N*-methylphenylglycine (12 mg, 0.045 mmol), diisopropylcarbodiimide (7 mL, 0.45 mmol) and 1-hydroxy-7-azabenzotriazole (6.1 mg, 0.45 mmol) in DMF (0.5 mL) and dichloromethane (0.5 mL) was stirred at room temperature for 16 hours. The reaction mixture was loaded onto an ion exchange cartridge (SCX, 0.5 g), washed with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), and 2 *M* NH_3 in methanol. The concentrated ammonia fractions

were collected and concentrated to give the desired product (10 mg).

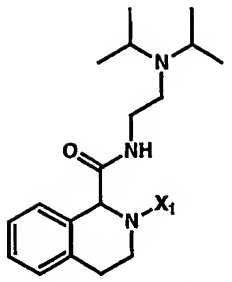
D.



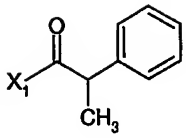
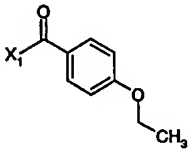
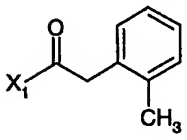
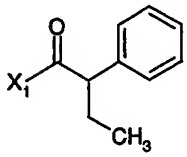
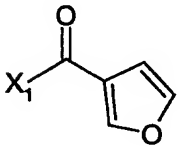
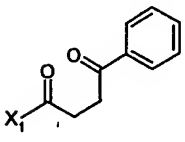
A solution of Part C compound (10 mg, 0.018 mmol) in 4 *M* HCl in dioxane (0.4 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated to give the desired product as an oil (11 mg): HPLCb rt=1.77 and 2.0 min; LC/MS (electrospray, + ions) m/z 451.5 (M+H).

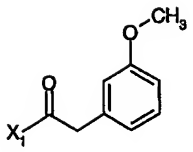
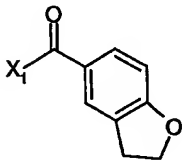
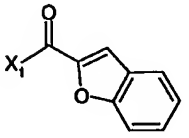
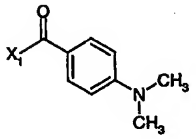
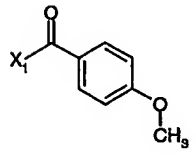
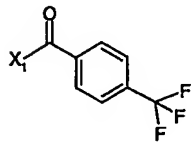
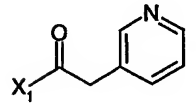
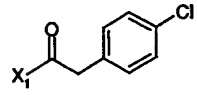
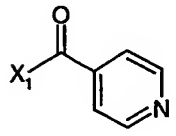
Examples 439-486

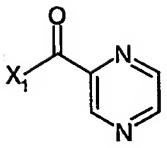
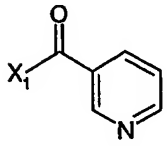
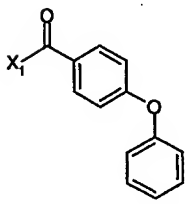
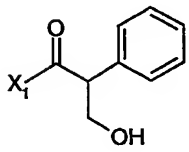
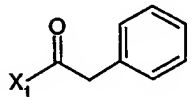
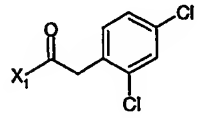
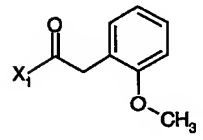
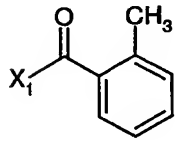
The compounds shown in the table below were synthesized in library format starting with Part B compound from Example 109. Part B compound from Example 109 (500 µL of a 0.06 *M* solution in dichloromethane, 0.03 mmol), the appropriate acid (300 µL of a 0.15 *M* solution in dichloromethane, 0.045 mmol), 1-hydroxy-7-azabenzotriazole (0.045 mmol), and diisopropylcarbodiimide (0.045 mmol) in 200 µL DMF were stirred at room temperature for 16 hours. The reaction mixtures were loaded onto ion exchange cartridges (SCX, 0.5 g), washed with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), and 2 *M* NH_3 in methanol. The concentrated ammonia fractions were collected and concentrated to give the desired products which gave the analytical data shown.

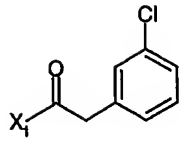
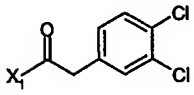
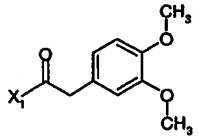
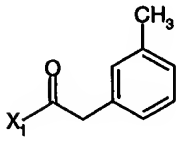
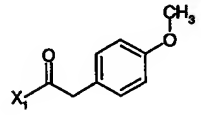
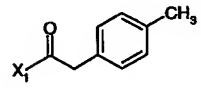
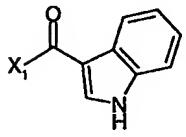
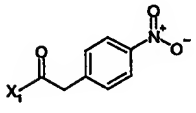
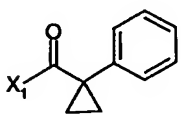


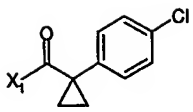
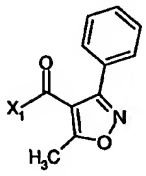
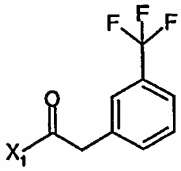
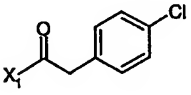
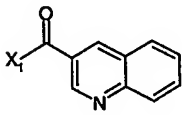
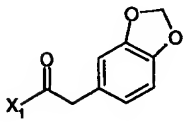
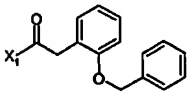
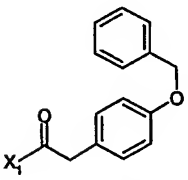
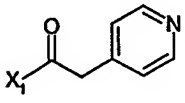
= X_1-R_1

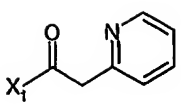
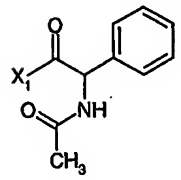
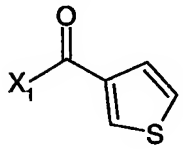
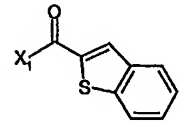
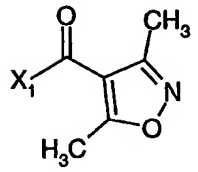
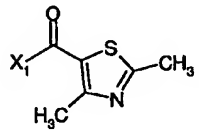
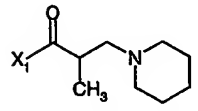
Example No.	X_1-R_1	Calc MW	LC/MS $(M + H)^+$
439		435.61	436.5
440		451.6	452.61
441		435.6	436.61
442		449.6	450.62
443		397.5	398.54
444		463.6	464.61

445		451.6	452.61
446		449.6	450.58
447		447.6	448.57
448		450.6	451.63
449		437.6	438.59
450		475.6	476.57
451		422.6	423.6
452		497.2	498.57
453		408.6	409.61

454		409.5	410.57
455		408.6	409.59
456		499.7	500.61
457		451.6	452.63
458		421.6	422.59
459		489.2	490.52
460		451.6	452.6
461		421.6	422.59

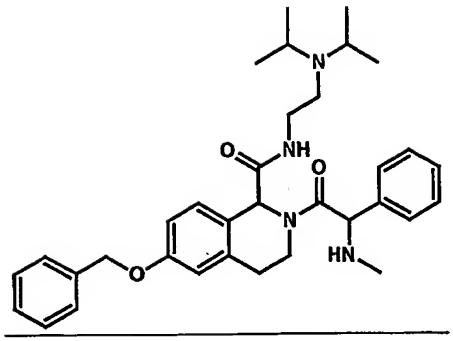
462		455.2	456.56
463		489.2	490.53
464		481.6	482.62
465		435.6	436.61
466		451.6	452.6
467		435.6	436.62
468		446.6	447.59
469		466.6	467.57
470		447.6	448.63

471		481.3	482.58
472		488.6	489.62
473		489.6	490.59
474		455.2	456.57
475		458.6	459.49
476		465.6	466.61
477		527.7	528.63
478		527.7	528.64
479		422.6	423.59

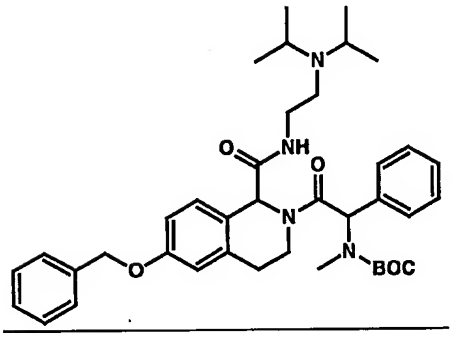
480		422.6	423.49
481		478.6	479.52
482		413.6	414.55
483		463.6	464.57
484		426.6	427.59
485		442.6	443.56
486		456.7	457.58

Example 487

Isomer A and Isomer B

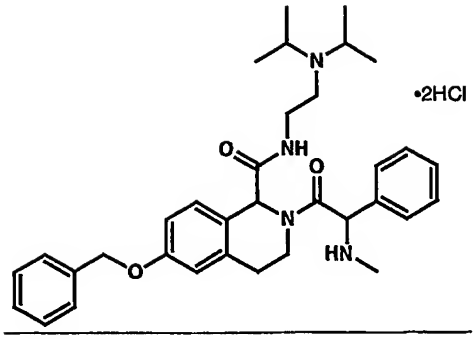


A.



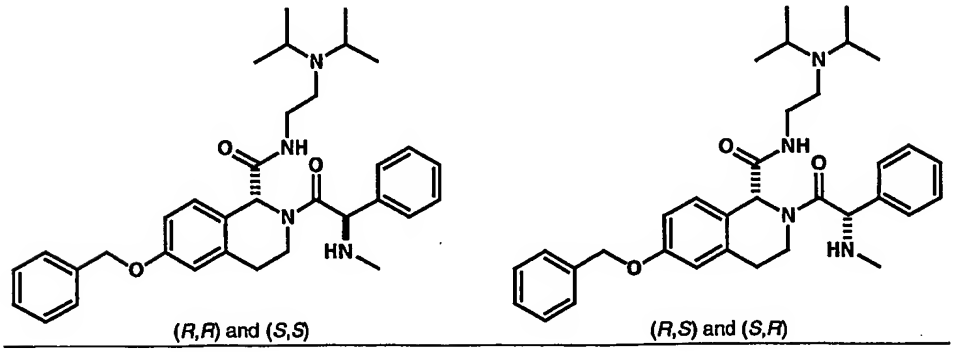
A solution of Part A compound from Example 64 (0.25 g, 0.60 mmol), *N*-BOC-*N*-methylphenylglycine (0.24 g, 0.90 mmol), diisopropylcarbodiimide (143 µL, 0.90 mmol) and 1-hydroxy-7-azabenzotriazole (0.12 g, 0.90 mmol) in DMF (2 mL) and dichloromethane (2 mL) was stirred at room temperature for 16 hours. The reaction mixture was loaded onto an ion exchange cartridge (SCX, 0.5 g), washed with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), and 2 *M* NH_3 in methanol. The concentrated ammonia fractions were collected and concentrated to give the desired product (0.1 g).

B.



A solution of Part A compound (130 mg, 0.20 mmol) in 4 *M* HCl in dioxane (2 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated to give the desired product as a light brown solid (11 mg): HPLCb rt=2.44 and 2.68 min; LC/MS (electrospray, + ions) m/z 557.5 (M+H).

Example 488 and 489

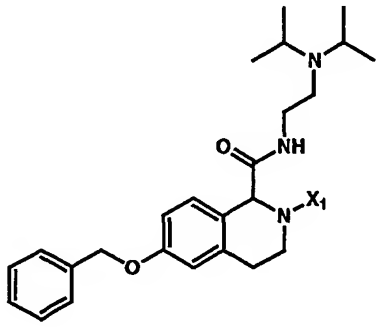


A sample of Part B compound from Example 487 (0.6 g) was purified using preparative chromatography and the two bands corresponding to the diastereomer pairs were isolated. The material in each band was isolated from the fractions by loading the corresponding fractions onto an ion exchange cartridge (SCX, 0.5 g), washing with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), and 2 *M* NH_3 in methanol. The concentrated ammonia fractions were collected and concentrated to give the desired

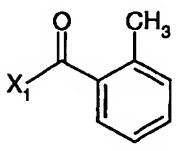
product. Isomer pair A (110 mg) : HPLCb rt=2.71 min; LC/MS (electrospray, + ions) m/z 557.5 (M+H); Isomer pair B (80 mg) : HPLCb rt=2.90 min; LC/MS (electrospray, + ions) m/z 557.5 (M+H).

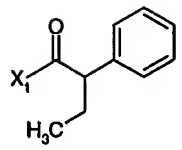
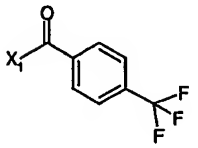
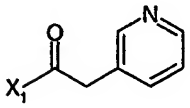
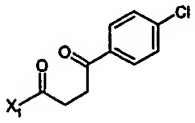
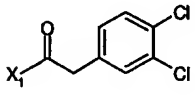
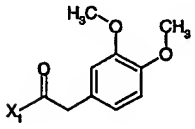
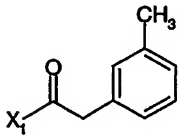
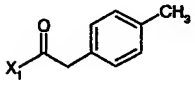
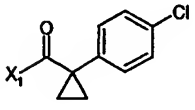
Examples 490-503

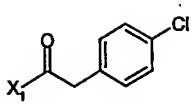
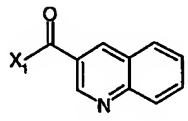
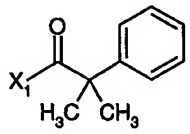
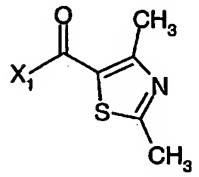
The compounds shown in the table below were synthesized in library format starting with Part A compound from Example 7. Part A compound from Example 7 (500 µL of a 0.06 *M* solution in dichloromethane, 0.03 mmol), the appropriate acid (300 µL of a 0.15 *M* solution in dichloromethane, 0.045 mmol), 1-hydroxy-7-azabenzotriazole (0.045 mmol), and diisopropylcarbodiimide (0.045 mmol) in 200 µL DMF were stirred at room temperature for 16 hours. The reaction mixtures were loaded onto ion exchange cartridges (SCX, 0.5 g), washed with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), and 2 *M* NH_3 in methanol. The concentrated ammonia fractions were collected and concentrated to give the desired products which gave the analytical data shown.



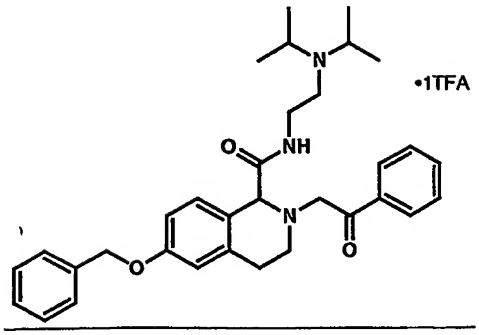
= X_1-R_1

Example No	X_1-R_1	Calc MW	LC/MS $(M + H)^+$
490		527.7	528.74

491		555.8	556.78
492		581.7	582.72
493		528.7	529.74
494		603.3	604.72
495		595.2	596.67
496		587.8	588.76
497		541.7	542.76
498		541.7	542.75
499		587.3	588.71

500		561.3	562.7
501		564.7	565.74
502		555.8	556.78
503		548.8	549.73

Example 504

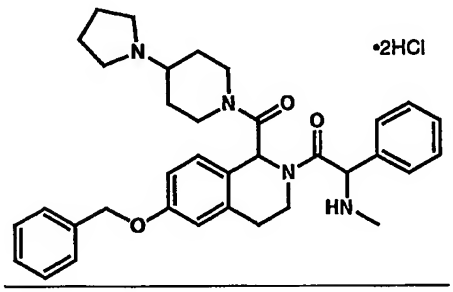


To a solution of Part A compound from Example 64 (50 mg, 0.12 mmol) and 2-bromoacetophenone (26 mg, 0.13 mmol) in acetone (2 mL) was added potassium carbonate (0.15 g) and the mixture was stirred at room temperature for 16 hours. The solution was diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to give the crude product. Some of this product was purified

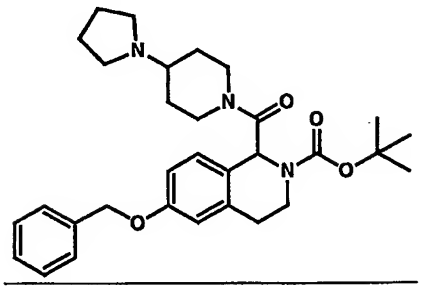
using preparative HPLC to give the trifluroacetate salt (6.5 mg): HPLCb rt=2.71; LC/MS (electrospray, + ions) m/z 528.47 (M+H).

Example 505

Isomer A and Isomer B

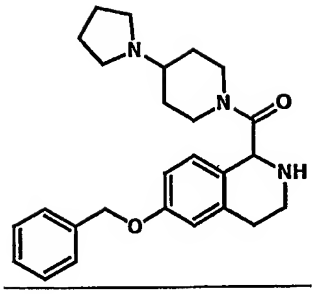


A.



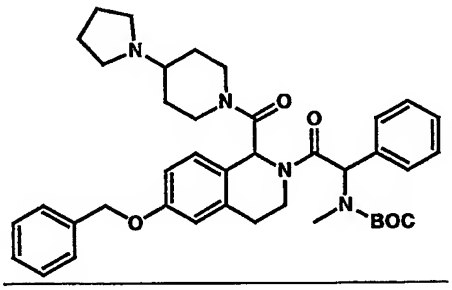
To a solution of Part E compound from Example 1 (0.6 g, 1.56 mmol), 4-(1-pyrrolidinyl)piperidine (0.29 g, 1.9 mmol), and 1-hydroxy-7-azabenzotriazole (0.21 g, 1.9 mmol) in DMF (3 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.3 g, 1.9 mmol) and the mixture was stirred at room temperature for 20 hours. The reaction mixture was loaded onto an ion exchange cartridge (SCX, 0.5 g), washed with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), and 2 *M* NH_3 in methanol. The concentrated ammonia fractions were collected and concentrated to give the desired product (0.7 g).

B.



Part A compound (0.7 g, 1.3 mmol) was dissolved in 4 *M* HCl in dioxane (1 mL) and stirred at room temperature for 1 hour. Concentration in vacuo gave the crude hydrochloride salt. The reaction mixture was loaded onto an ion exchange cartridge (SCX, 0.5 g), washed with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), and 2 *M* NH_3 in methanol. The concentrated ammonia fractions were collected and concentrated to give the desired product (0.5 g).

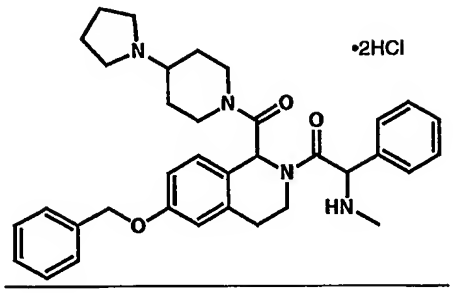
C.



A solution of Part B compound (0.1 g, 0.24 mmol), *N*-BOC-*N*-methylphenylglycine (76 mg, 0.28 mmol), diisopropylcarbodiimide (45 µL, 0.28 mmol) and 1-hydroxy-7-azabenzotriazole (39 mg, 0.28 mmol) in DMF (2 mL) and dichloromethane (2 mL) was stirred at room temperature for 16 hours. The reaction mixture was loaded onto an ion exchange cartridge (SCX, 0.5 g), washed with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), and 2 *M* NH_3 in methanol. The concentrated ammonia fractions were collected and concentrated to give the crude product. This was further purified using chromatography (silica

gel, 10% methanol/dichloromethane) to give the desired product (0.1 g).

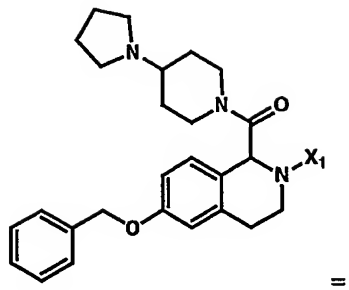
D.



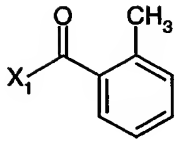
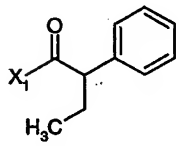
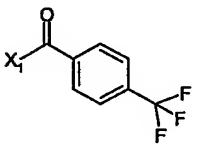
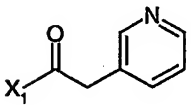
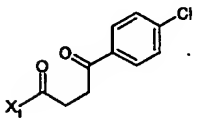
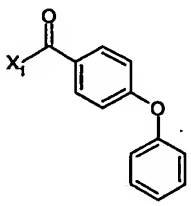
A solution of Part C compound (250 mg, 0.37 mmol) in 4 *M* HCl in dioxane (1 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated to give the crude product (200 mg): HPLCb rt=2.45 and, 2.66 min; LC/MS (electrospray, + ions) m/z 567.5 (M+H).

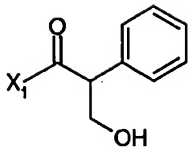
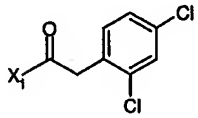
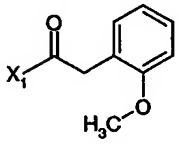
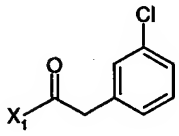
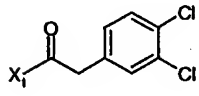
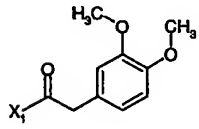
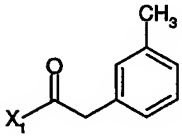
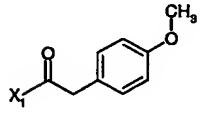
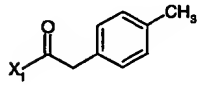
Examples 506-528

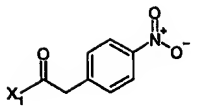
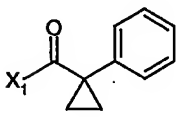
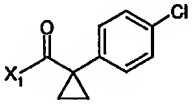
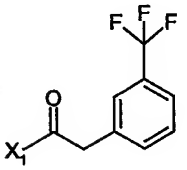
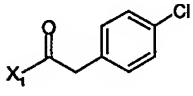
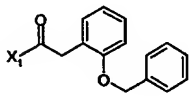
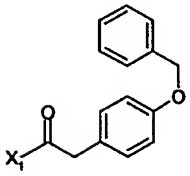
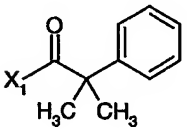
The compounds shown in the table below were synthesized in library format starting with Part B compound from Example 505. Part B compound from Example 505 (500 µL of a 0.06 *M* solution in dichloromethane, 0.03 mmol), the appropriate acid (300 µL of a 0.15 *M* solution in dichloromethane, 0.045 mmol), 1-hydroxy-7-azabenzotriazole (0.045 mmol), and diisopropylcarbodiimide (0.045 mmol) in 200 µL DMF were stirred at room temperature for 16 hours. The reaction mixtures were loaded onto ion exchange cartridges (SCX, 0.5 g), washed with methanol (2x1.5 mL), 0.1 *N* NH_3 in methanol (2x1.5 mL), and 2 *M* NH_3 in methanol. The concentrated ammonia fractions were collected and concentrated to give the desired products which gave the analytical data shown.



= X_1-R_1

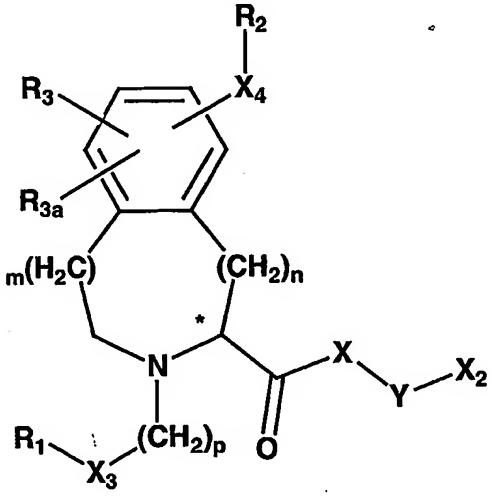
Example No	X_1-R_1	Calc MW	LC/MS $(M + H)^+$
506		537.7	538.71
507		565.8	566.77
508		591.7	592.7
509		538.7	539.73
510		613.3	614.71
511		615.8	616.73

512		567.7	568.75
513		605.2	606.19
514		567.7	568.3
515		571.3	572.71
516		605.2	606.65
517		597.8	598.76
518		551.7	552.74
519		567.7	568.74
520		551.7	552.73

521		582.7	583.25
522		563.7	564.74
523		597.3	598.26
524		605.7	606.25
525		571.3	572.69
526		643.8	644.79
527		643.8	644.77
528		565.8	566.31

We claim:

1. A method of treating chemokinereceptor-mediated disorders comprising administering to a patient in need thereof a therepeutically effective amount of at least one compound of formula I



I

including enantiomers, diastereomers, and salts thereof, wherein

R_1 is alkyl, aryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, cycloalkyl,arylcycloalkyl cycloalkylalkyl, cycloalkyl-alkoxy, alkoxyalkyl, alkylthioalkyl, aryloxyalkyl, arylalkoxyalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, or heteroarylalkyl, and where these groups may be optionally substituted with 1 to 3 J1 groups which may be the same or different and the R_1 aryls may be further optionally substituted with 1 to 5 halogens, aryl, $-CF_3$, $-OCF_3$, 1-3 hydroxyls, 2 of which substituents where possible, may be joined by a methylene bridge;

R_2 is H, alkyl, aryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, aryloxyalkyl, arylalkoxyalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkylalkoxy, heteroaryl, or heteroarylalkyl, and where these groups may be optionally substituted with a J1a group and the aryls may be further

optionally substituted with 1 to 5 halogens, $-CF_3$, $-OCF_3$, or 1-3 hydroxyls;

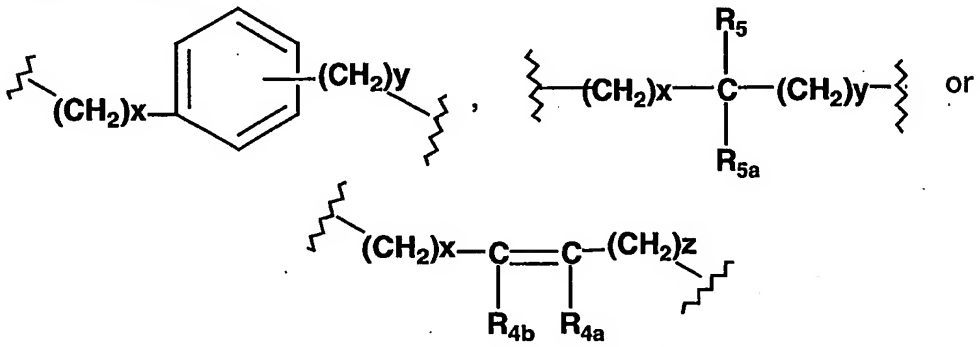
X is a bond, -O-, or $-NR_4-$;

R_3 and R_{3a} are the same or different and are independently selected from H, alkoxy, halogen, $-CF_3$, alkyl, or aryl;

R_4, R_{4a}, R_{4b}, R_{4c}, R_{4d}, R_{4e}, R_{4f}, R_{4g}, R_{4h}, R_{4i}, R_{4j}, R_{4k}, and R_{4l} are the same or different and are independently selected from H, C_1-C_6alkyl, or aryl;

m, n and p are the same or different and are independently 0 or 1;

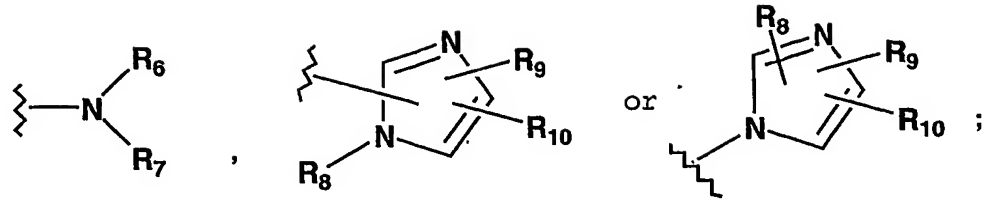
Y is a bond,



where x and y are the same or different and are independently 0 to 3 and z is 1 to 3;

R_5 and R_{5a} are the same or different and are independently H, alkyl, alkoxy, hydroxyl, halogen, $-CF_3$, aryl, alkaryl, and cycloalkyl; or R_5 and R_{5a} can be independently joined to one or both of R_6 and R_7 groups (see X_2) to form an alkylene bridge of 1 to 5 carbon atoms; or R_5 and R_{5a} can be joined together to form a ring of from 4-7 carbon atoms;

X_2 is aryl optionally substituted with 1 to 3 J1 groups which may be the same or different, cycloheteroalkyl optionally substituted with 1 to 3 J1 groups which may be the same or different, pyridinyl optionally substituted with 1 to 3 J1 groups which may be the same or different,



R_6 and R_7 are the same or different and are independently H or alkyl where the alkyl may be optionally substituted with halogen, 1 to 3 hydroxys, 1 to 3 C_1-C_{10}alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, or C_1-$_6$alkoxycarbonyl; or R_6 and R_7 can together form $-(CH_2)_tX_5(CH_2)_u-$ where X_5 is $-C(R_{4c})(R_{4d})-$, $-C(R_{4c})(NT_1T_{1a})-$, -O- or $-N(R_{4e})-$, t and u are the same or different and are independently 0 to 4;

R_8 is H, C_1-C_6alkyl, $-CF_3$, alkaryl, or aryl, and with the alkyl and aryl groups being optionally substituted with 1 to 3 hydroxys, 1 to 3 C_1-C_{10}alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy or C_1-C_6alkoxycarbonyl;

R_9 and R_{10} are the same or different and are independently H, C_1-C_6alkyl, $-CF_3$, alkaryl, aryl, or halogen, and with the alkyl and aryl groups being optionally substituted with 1 to 3 hydroxys, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-$_6$ alkoxy, phenyl, phenoxy or C_1-C_6 alkoxycarbonyl;

X_3 is a bond, $-C(O)-$, $-C(O)O-$, $-C(O)N(R_{4f})-$, $-S(O)_2-$, or $-S(O)_2N(R_{4f})-$;

X_4 is a bond, -O-, $-OC(O)-$, $-N(R_{4g})-$, $-N(R_{4g})C(O)-$, $-N(R_{4g})C(O)N(R_{4h})-$, $-N(R_{4g})S(O)_2-$, $-N(R_{4g})S(O)_2N(R_{4h})$, $-OC(O)N(R_{4g})-$, $-C(O)-$, $-C(O)N(R_{4g})-$, -S-, $-S(O)_2-$, or $-S(O)_2N(R_{4g})-$;

J1 and J1a are the same or different and are independently nitro, halogen, hydroxyl, $-OCF_3$, $-CF_3$, alkyl, aryl, $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vN(T_{1a})C(O)OT_1$, $-(CH_2)_vN(T_{1a})C(O)N(T_{1a})T_1$, $-(CH_2)_vNT_1(T_{1a})$, $-(CH_2)_vN(T_{1a})SO_2T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)N(T_{1a})T_1$, $-(CH_2)_vN(T_{1a})SO_2N(T_{1b})T_1$,

$-(CH_2)_vOT_1$, $-(CH_2)_vSO_2T_1$, $-(CH_2)_vSO_2N(T_{1a})T_1$, $-(CH_2)_vC(O)T_1$, $-(CH_2)_vCH(OH)T_1$, or heteroaryl as defined below, with v being 0-3;

T_1, T_{1a} and T_{1b} are the same or different and are independently H, alkyl, alkenyl, alkynyl, lower alkythioalkyl, alkoxyalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, or cycloalkyl, each of which may be optionally substituted with halogen, hydroxyl, $-C(O)NR_{4i}R_{4j}$, $-NR_{4i}C(O)R_{4j}$, -CN, $-N(R_{4i})SO_2R_{11}$, $-OC(O)R_{4i}$, $-SO_2NR_{4i}R_{4j}$, $-SOR_{11}$, $-SO_2R_{11}$, alkoxy, -COOH, cycloheteroalkyl, or $-C(O)OR_{11}$; with the proviso that T_1 cannot be hydrogen when it is connected to sulfur, as in SO_2T_1; or T_1 and T_{1a} or T_1 and T_{1b} can together form $-(CH_2)_rX_{5a}(CH_2)_s-$ where X_{5a} is $-C(R_{4k})(R_{4l})-$, $-C(R_{4k})(NT_1T_{1a})-$, -O- or $-N(R_{4k})-$, r and s are the same or different and are independently 0 to 4;

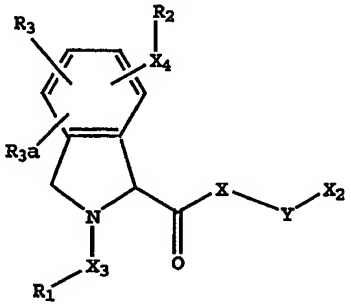
R_{11} is C_1-C_6alkyl or aryl;

with the proviso that

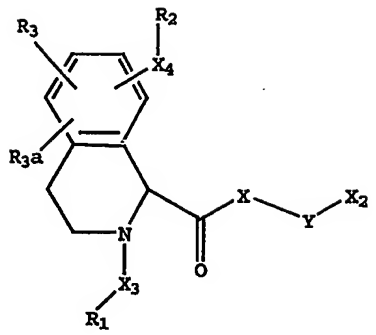
(1) where m is 0 and n is 1, the moiety $-X_4-R_2$ is other than alkyl or alkoxy; and

(2) where X is a bond and X_2 is amino, then m is 1.

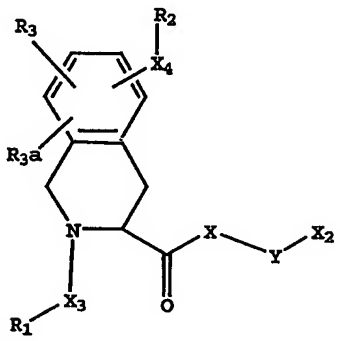
2. The method of claim 1 wherein the compound of formula I has the structure



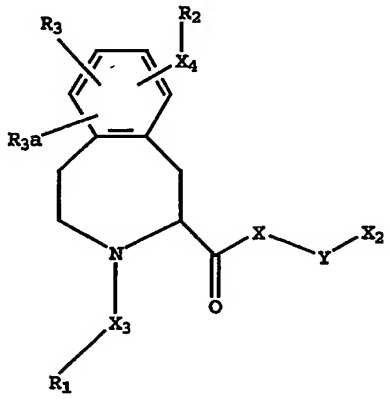
3. The method of claim 1 wherein the compound of formula I has the structure



4. The method of claim 1 wherein the compound of formula I has the structure



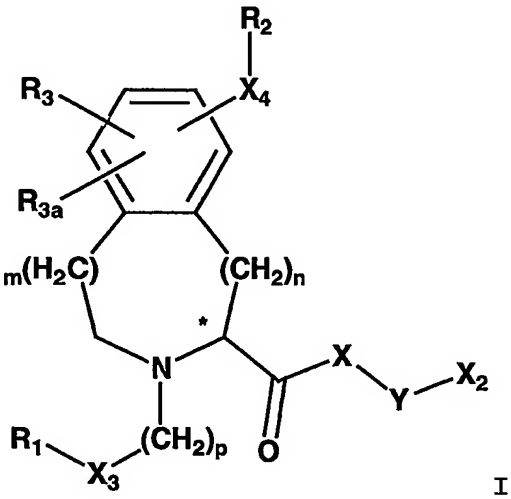
5. The method of claim 1 wherein the compound of formula I has the structure



6. The method of any one of claims 1-5 wherein the chemokine receptor-mediated disorder is selected from asthma, COPD, allergic disease, allergic rhinitis,

rheumatoid arthritis, atherosclerosis, psoriasis, solid organ transplant rejection, osteoarthritis and inflammatory bowel syndrome.

7. A compound of formula I



I

including enantiomers, diastereomers, and salts thereof, wherein

R_1 is alkyl, aryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, cycloalkyl,arylcycloalkyl cycloalkylalkyl, cycloalkyl-alkoxy, alkoxyalkyl, alkylthioalkyl, aryloxyalkyl, arylalkoxyalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, or heteroarylalkyl, and where these groups may be optionally substituted with 1 to 3 J1 groups which may be the same or different and the R_1 aryls may be further optionally substituted with 1 to 5 halogens, aryl, $-CF_3$, $-OCF_3$, 1-3 hydroxyls, 2 of which substituents where possible, may be joined by a methylene bridge;

R_2 is H, alkyl, aryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, aryloxyalkyl, arylalkoxyalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkylalkoxy, heteroaryl, or heteroarylalkyl, and where these groups may be optionally substituted with a J1a group and the aryls may be further

optionally substituted with 1 to 5 halogens, $-CF_3$, $-OCF_3$, or 1-3 hydroxyls;

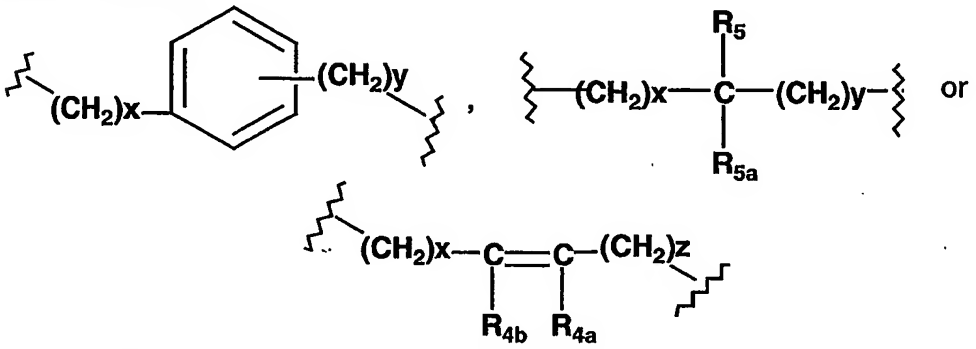
X is a bond, -O-, or $-NR_4-$;

R_3 and R_{3a} are the same or different and are independently selected from H, alkoxy, halogen, $-CF_3$, alkyl, or aryl;

R_4, R_{4a}, R_{4b}, R_{4c}, R_{4d}, R_{4e}, R_{4f}, R_{4g}, R_{4h}, R_{4i}, R_{4j}, R_{4k}, and R_{4l} are the same or different and are independently selected from H, C_1-C_6alkyl, or aryl;

m, n and p are the same or different and are independently 0 or 1;

Y is a bond,



where x and y are the same or different and are independently 0 to 3 and z is 1 to 3;

R_5 and R_{5a} are the same or different and are independently H, alkyl, alkoxy, hydroxyl, halogen, $-CF_3$, aryl, alkaryl, and cycloalkyl; or R_5 and R_{5a} can be independently joined to one or both of R_6 and R_7 groups (see X_2) to form an alkylene bridge of 1 to 5 carbon atoms; or R_5 and R_{5a} can be joined together to form a ring of from 4-7 carbon atoms;

X_2 is aryl optionally substituted with 1 to 3 J1 groups which may be the same or different, cycloheteroalkyl optionally substituted with 1 to 3 J1 groups which may be the same or different, or pyridinyl optionally substituted with 1 to 3 J1 groups which may be the same or different;

R_6 and R_7 are the same or different and are independently H or alkyl where the alkyl may be optionally substituted with halogen, 1 to 3 hydroxys, 1

to 3 C_1-C_{10}alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, or C_1-$_6$alkoxycarbonyl; or R_6 and R_7 can together form $-(CH_2)_tX_5(CH_2)_u-$ where X_5 is $-C(R_{4c})(R_{4d})-$, $-C(R_{4c})(NT_1T_{1a})-$, -O- or $-N(R_{4e})-$, t and u are the same or different and are independently 0 to 4;

R_8 is H, C_1-C_6alkyl, $-CF_3$, alkaryl, or aryl, and with the alkyl and aryl groups being optionally substituted with 1 to 3 hydroxys, 1 to 3 C_1-C_{10}alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy or C_1-C_6alkoxycarbonyl;

R_9 and R_{10} are the same or different and are independently H, C_1-C_6alkyl, $-CF_3$, alkaryl, aryl, or halogen, and with the alkyl and aryl groups being optionally substituted with 1 to 3 hydroxys, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-$_6$ alkoxy, phenyl, phenoxy or C_1-C_6 alkoxycarbonyl;

X_3 is a bond, $-C(O)-$, $-C(O)O-$, $-C(O)N(R_{4f})-$, $-S(O)_2-$, or $-S(O)_2N(R_{4f})-$;

X_4 is a bond, -O-, $-OC(O)-$, $-N(R_{4g})-$, $-N(R_{4g})C(O)-$, $-N(R_{4g})C(O)N(R_{4h})-$, $-N(R_{4g})S(O)_2-$, $-N(R_{4g})S(O)_2N(R_{4h})$, $-OC(O)N(R_{4g})-$, $-C(O)-$, $-C(O)N(R_{4g})-$, -S-, $-S(O)_2-$, or $-S(O)_2N(R_{4g})-$;

J1 and J1a are the same or different and are independently nitro, halogen, hydroxyl, $-OCF_3$, $-CF_3$, alkyl, aryl, $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vN(T_{1a})C(O)OT_1$, $-(CH_2)_vN(T_{1a})C(O)N(T_{1a})T_1$, $-(CH_2)_vNT_1(T_{1a})$, $-(CH_2)_vN(T_{1a})SO_2T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)N(T_{1a})T_1$, $-(CH_2)_vN(T_{1a})SO_2N(T_{1b})T_1$, $-(CH_2)_vOT_1$, $-(CH_2)_vSO_2T_1$, $-(CH_2)_vSO_2N(T_{1a})T_1$, $-(CH_2)_vC(O)T_1$, $-(CH_2)_vCH(OH)T_1$, or heteroaryl as defined below, with v being 0-3;

T_1, T_{1a} and T_{1b} are the same or different and are independently H, alkyl, alkenyl, alkynyl, lower alkythioalkyl, alkoxyalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, or cycloalkyl, each of which may be optionally substituted with halogen, hydroxyl, -C(O)NR4iR4j, -NR4iC(O)R4j, -CN,-N(R4i)SO2R11,

$-OC(O)R_{4i}$, $-SO_2NR_{4i}R_{4j}$, $-SOR_{11}$, $-SO_2R_{11}$, alkoxy, -COOH, cycloheteroalkyl, or $-C(O)OR_{11}$; with the proviso that T_1 cannot be hydrogen when it is connected to sulfur, as in SO_2T_1; or T_1 and T_{1a} or T_1 and T_{1b} can together form $-(CH_2)_rX_{5a}(CH_2)_s-$ where X_{5a} is $-C(R_{4k})(R_{41})-$, $-C(R_{4k})(NT_1T_{1a})-$, -O- or $-N(R_{4k})-$, r and s are the same or different and are independently 0 to 4;

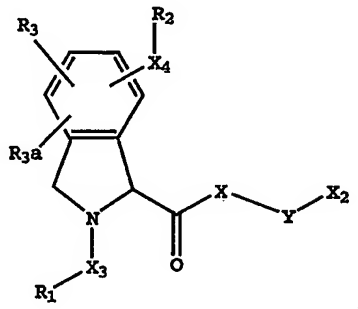
R_{11} is C_1-C_6alkyl or aryl;

with the proviso that

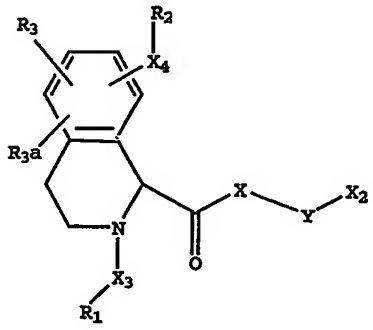
(1) where m is 0 and n is 1, the moiety $-X_4-R_2$ is other than alkyl or alkoxy; and

(2) where X is a bond and X_2 is amino, then m is 1.

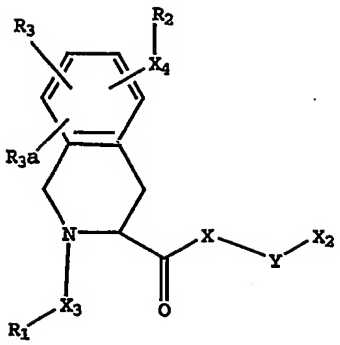
8. A compound of claim 7 having the structure



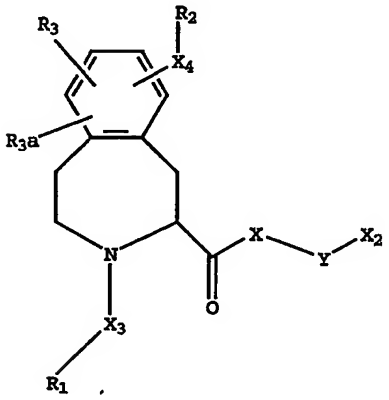
9. A compound of claim 7 having the structure



10. A compound of claim 7 having the structure



11. A compound of claim 7 having the structure



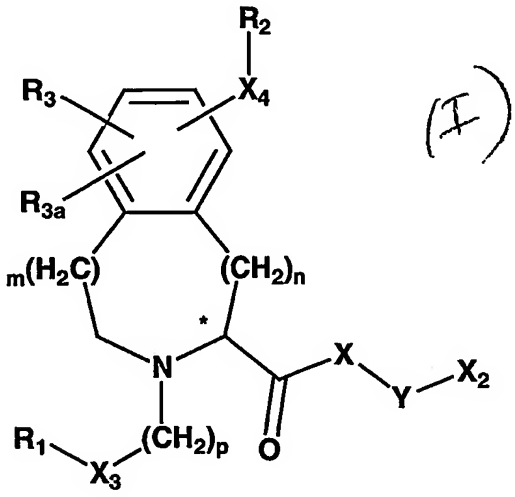
12. A pharmaceutical composition comprising at least one compound of any one of claims 7-12 and a pharmaceutically acceptable vehicle or carrier therefor.

TETRAHYDROISOQUINOLINE ANALOGS AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

Abstract of the Disclosure

Tetrahydroisoquinoline analogs are provided which are modulators of chemokine receptor activity.

The tetrahdroisoquinoline analogs thereof have the structure



(I)

wherein R_1, R_2, R_3, R_{3a}, X_1, X_2, X_3, X_4, m, n and p are as described herein.